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Metformin: An Anti-diabetic Drug with Multiple Clinical Applications

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ABSTRACT:
Metformin the anti-diabetic and oral hypoglycaemic agent is the first-choice drug for the treatment of type 2 diabetes and polycystic ovary disease. Also, recent studies suggest that patients with several forms of cancer benefits with metformin treatment. It shows the wide range of therapeutic application in dermatology. As it plays important role in improving hyperinsulinemia, it has improved the condition of hormonal acne and acanthosis nigricans. Interestingly, it has also been used topically for hyperpigmentation and this is the most recent dermatologic indication of metformin.This review article covers the pharmacokinetic and pharmacodynamic of drug. Also includes drug interaction and mechanism of action of drug in various disease conditions.

KEYWORDS: Metformin, Anti-diabetic, Dermatology, Anticancer, Pharmacokinetic.

I. INTRODUCTION:

[1, 2]. Metformin and the related drug phenformin (the latter of which has been withdrawn from diabetes treatment in most countries due to lactic acidosis side effects) are derived from galegine, a natural product derived from the plant Galega officinalis, which was used in mediaeval European herbal medicine. In the 1920s, galegine was studied in humans as a glucose-lowering drug, but it was determined to be too toxic. Two synthetic derivatives of galegine, metformin and phenformin, were initially synthesised and investigated around the same period, however they were not used in clinical trials until the 1950s.Galegine is an isoprenyl guanidine derivative, whereas metformin and phenformin are biguanides that comprise two linked guanidine molecules with extra substitutions. Metformin, unlike other modern medications, is derived from a natural product used in herbal therapy and was not created to target a specific illness pathway or mechanism. It was established as a safe and effective medication before extensive mechanistic studies were possible, and its molecular mechanisms of action are still hotly contested after 60 years of clinical use.Galegine is an isoprenyl guanidine derivative, whereas metformin and phenformin are biguanides that comprise two linked guanidine molecules with extra substitutions.

Metformin, unlike other modern medications, is derived from a natural product used in herbal therapy and was not created to target a specific illness pathway or mechanism. [2]. It was established as a safe and effective medication before extensive mechanistic studies were possible, and its molecular mechanisms of action are still hotly contested after 60 years of clinical use.[3, 4]. Metformin was first approved in Canada in 1972, and received subsequent FDA approval in the US in 1995. A medication that is used to treat diabetes mellitus (a condition in which the body cannot control the level of sugar in the blood). It's also being researched as a cancer treatment. Metformin hydrochloride, a biguanide antihyperglycemic drug which reduces the quantity of glucose (a type of sugar) produced in the bloodstream by the liver while increasing glucose utilisation by the organism in people with type 2 diabetes.[4]. It is first-line pharmacotherapy for type 2 diabetes.It is also used to treat insulin resistance in polycystic ovarian syndrome (PCOS). Metformin hydrochloride contains the active component metformin. Also known as "glucophage."

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II. METFORMIN AND GASTROINTESTINAL TRACT:

[5, 6]. Metformin uptake is saturable and dose-dependent, which supports the hypothesis that it is mostly dependent on transporters. Metformin is efficiently taken up across the apical surface of enterocytes via bidirectional transporters, but efflux across the basolateral surface of enterocytes is limited, resulting in metformin accumulation in the epithelium, possibly accounting for the greatly increased metformin concentration seen in these cells, according to studies in Caco-2 cell monolayers (a cellular model of human intestinal epithelium).

Some paracellular uptake was proposed to explain the presence of metformin in the portal circulation, with metformin diffusing passively. Organic cation transporter (OCT) 1–3,plasma membrane monoamine transporter (PMAT), multidrug and toxin extrusion protein (MATE) 1–2, serotonin transporter (SERT), and high-affinity choline transporter are among the transporters forwhich metformin is a potential substrate (CHT).[7]. OCTsare members of the SLC22 (solute carrier family 22) gene, which was first discovered in 1994 and is located on chromosome 6q26. OCTs are found in the colon, liver, kidneys, brain, muscle, and heart, among other tissues. [8]. OCT1 is primarily expressed in the liver, although it is critical in the transfer of cations from the gut lumen to the interstitium, including metformin. [9, 10, 11]. OCT1 was formerly thought to be found on the basolateral membrane, however more recent studies have shown it on the apical surface of intestinal epithelial cells. [8]. OCT2 is mostly expressed in the kidney and is involved in metformin excretion via the kidney. OCT3 is mostly found in skeletal muscle, but it is also found in the colon. [12]. OCT3 is linked to metformin absorption and efflux in the salivary glands, which could explain the dysgeusia that comes with metformin treatment. [13, 14]. PMAT was discovered to be a monoamine transporter belonging to the equilibrative nucleoside transporter (ENT) family, which is located mostly in the brain and central nervous system. PMAT was eventually discovered to be polyspecific, residing in a variety of tissues throughout the body, including the gut, where it transports metformin with a similar affinity to OCTs. [15]. PMAT is found near the tips of the mucosal epithelial layer, implying that it is involved in metformin absorption.

[16]. Table 1Membrane transporters involved in metformin pharmacokinetics

METFORMIN TRANSPORTER	ENCODED BY	FUNCTION
SLC22A1 (also known as OCT1)	SLC22A1	Main transporter accountable for metformin uptake18 Expressed in liver and kidney Some SNPs shown to associate with reduced metformin uptake, increased metformin elimination as a result of reduced renal tubular reabsorption and lower therapeutic response owing to diminished action of metformin in the liver144 Wide disparity in frequency distribution of SNPs among ethnic groups18
SLC22A2 (also known as OCT2)	SLC22A	Mediates metformin secretion (kidney) Accountable for 80% of the total metformin clearance85
SLC22A3 (also known as OCT3)	SLC22A3	Expressed in multiple tissues (including liver, kidney, heart, skeletal muscle, brain, placenta) May be important in the uptake of metformin in muscle145
SLC22A4 (also known as OCTN1)	SLC22A4	Involved in the gastrointestinal absorption of metformin146 Role in the mitochondrial uptake of phenformin17
MATE1	SLC47A1	Mediates metformin secretion (kidney; liver–excretion into bile) Rs2289669 polymorphism was associated with an amplified glucose-lowering effect of metformin in

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		diabetic patients147
MATE2	SLC47A2	Mediates metformin secretion (kidney
hENT4 (also known as PMAT)	SLC29A4	Mediates renal and intestinal metformin uptake148
Abbreviations: hENT4, equilibrative nucleotide transporter 4; MATE1, multidrug and toxin extrusion transporter 1; PMAT, plasma membrane monoamine transporter; SLC22A1, solute carrier family 22 member 1; SNP, single nucleotide polymorphism.		

III. PHARMACODYNAMICS

III.1 GENERAL EFFECTS:

[17, 18]. Insulin is a hormone that helps to keep blood glucose levels in control. Type II diabetes is marked by a loss of insulin sensitivity, resulting in blood glucose rises when the pancreas can no longer compensate. Insulin is unable to exert adequate effects on tissues and cells in patients with type 2 diabetes (i.e. insulin resistance), and insulin insufficiency may also be present.

[19]. Metformin lowers hepatic glucose synthesis, lowers intestinal glucose absorption, and improves insulin sensitivity by improving both peripheral glucose uptake and utilisation. In contrast to sulfonylurea medications, which cause hyperinsulinemia, metformin does not cause insulin production to increase.

III.2 EFFECT ON FASTING PLASMA GLUCOSE (FPG) AND GLYCOSYLATED HEAMOGLOBIN (HbA1c)

[19]. HbA1c is a glycaemic control test that is used to monitor diabetes patients on a regular basis. Fasting plasma glucose is another helpful and crucial glycaemic control indicator. Metformin reduced fasting plasma glucose levels by an average of 59 mg/dL from baseline in a 29-week clinical study of type II diabetic patients, compared to an average rise of 6.3 mg/dL in participants receiving a placebo. Glycosylated haemoglobin (HbA1c) was reduced by 1.4 percent in metformin-treated patients and increased by 0.4 percent in placebo-treated subjects.

IV. PHARMACOKINETICS

IV.1 ABSORPTION:

[17]. Metformin is used orally in doses ranging from 500 mg b.i.d. or t.i.d. to a maximum of 2,550 mg per day, or approximately 35 mg/kg/day. Following an oral dose of metformin, the immediate-release formulation is rapidly absorbed from the small intestine. It has a 1.5-hour onset of action, a 1.5–4.9-hour half-life in the circulatory system, and a 16–20-hour duration of action. [20]. The duodenum can absorb about 20% of a total dose, the jejunum and ileum up to 60%, while the colon can only absorb a very little quantity. The rest is passed through the faeces. [21]. Higher dosages cause slower absorption and lower bioavailability. [22]. In man, oral absorption of metformin from immediate-release dose formulations is inefficient, with an estimated population mean bioavailability of 55%. [23]. Metformin has a 40 to 60 percent absolute oral bioavailability, and gastrointestinal absorption appears to be complete within 6 hours of intake. [22]. Its hydrophilicity is linked to a low permeability of the intestinal and cell membranes, which is known to be a main limiting step in metformin oral absorption.

[17]. The extended-release version has a comparable onset of action, but it has a half-life of 6.5 hours and a 24-hour duration of action. As a result, it only needs to be taken once a day. When compared to the immediate-release formulation, it is associated with less gastrointestinal adverse effects. Metformin's half-life may be prolonged in patients with renal impairment, posing a theoretical risk of lactic acidosis, an uncommon but serious condition. It's been claimed that this danger arises from metformin's suppression of gluconeogenesis, which causes lactic acid metabolism in the liver to be inhibited, leading in lactate build up. [24]. Metformin absorption in the intestine may be mediated predominantly by the plasma membrane monoamine transporter (PMAT). However, there is no in-vivo evidence that PMAT plays a role in metformin distribution or pharmacological action.

IV.2 DISTRIBUTION:

[23]. Following absorption, metformin is rapidly disseminated and does not interact to plasma proteins. [25]. After intravenous administration, the volume of distribution has been observed to range from 63 to 276 L. [17, 26]. After a single therapeutic dose (20 mg/kg/day in humans or 250 mg/kg/day in mice), metformin

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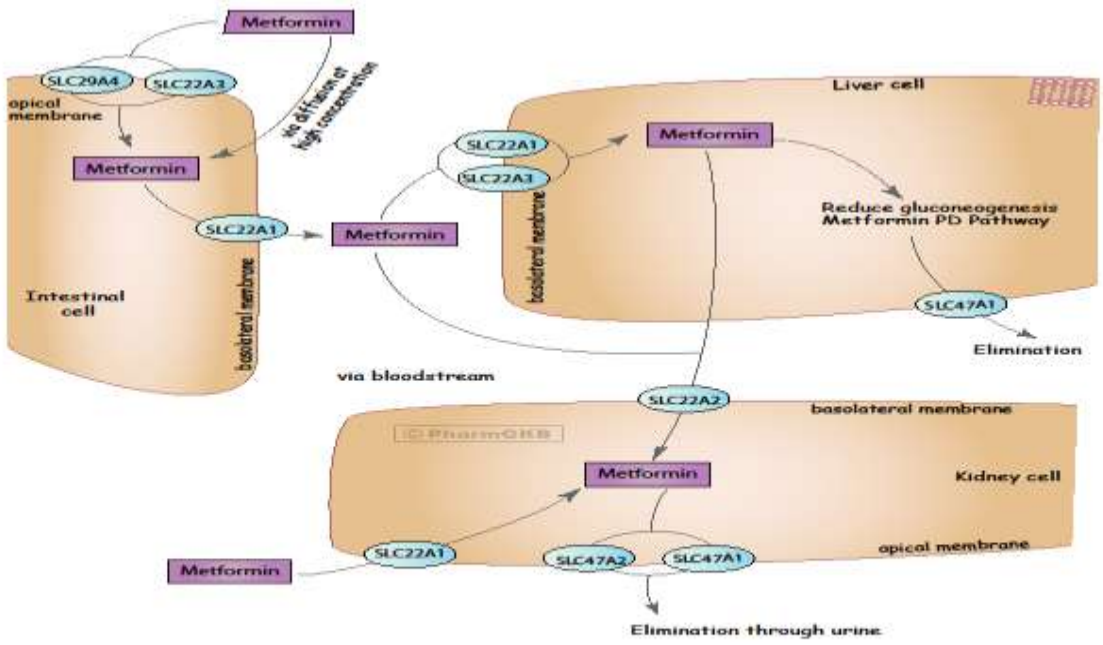
concentration in the liver is three to five times greater than that in the portal vein (40–70µmol/L), and metformin concentration in general circulation is 10–40 µmol/L. [27]. Metformin's antihyperglycemic impact is mostly owing to its suppression of hepatic glucose production, and metformin concentration in hepatocytes is significantly higher than in the blood, therefore the liver is thought to be the principal site of metformin function. [28]. Metformin steady-state plasma concentrations of 1 mcg/mL are obtained within 24 to 48 hours at standard clinical doses and dosing regimens of metformin hydrochloride tablets.

IV.3 METABOLISM AND ELIMINATION:

[8]. Metformin has a half-life of around 5 hours and is eliminated unaltered in the urine. The average renal clearance (CLr) in the population is 510+/-120 ml/min. Metformin is primarily eliminated through active tubular secretion in the kidney.Under steady-state conditions with 1gBID, the total amount of metformin excreted is roughly 6 mmol. The average faeces volume per 24 hours is 150 ml, with a calculated drug concentration of 40 mM in the distal colon. E. coli (with membrane potentials of 120 to 240 mV) may concentrate Metformin with subsequent block of its dihydrofolate reductase, so not all of it is free drug. The remaining 6 mmol enter the general circulation via the portal vein and are quickly removed by the kidneys after passing through the liver. The rate of plasma elimination, at 500 ml per minute, is comparable to the kidney plasma flow, indicating active secretion.

[29]. The low molecular weight associated with little plasma protein binding; the existence of transporters in the kidney; and the poor lipid solubility, which makes passive reabsorption negligible, are all likely contributors to metformin's high clearance. The clearance decreases in direct proportion to the loss of renal function. [30]. Metformin is not recommended if serum creatinine levels are less than 1.5 mg/dL in men and 1.4 mg/dL in women, or if creatinine clearance is irregular. It should not be started in people over the age of 80 unless creatinine clearance measurements show that renal function has not deteriorated.



[24]. Figure. 1Pharmacokinetics pathway of metformin. Stylized cells depicting genes involved in the transport and clearance of metformin. A fully interactive version is available online at http://www.pharmgkb.org/pathway/PA165948259. PD, pharmacodynamics.

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V. MECHANISM OF ACTION:

V.1 ANTIDIABETIC ACTION OF METFORMIN:

[16]. The antihyperglycemic action of drug is mainly a consequence of:

- Reduced glucose output by inhibition of liver gluconeogenesis with activation of AMPK,
- To lesser extent, increased insulin mediated glucose uptake,
- And has a little effect on glucose absorption through GIT but slightly delays the absorption process.

[7, 31].**Metformin and hepatic gluconeogenesis mitochondrial control** Hepatocytes must balance the demand for ATP with supply, which is predominantly provided by mitochondria, because gluconeogenesis is an energy-intensive process (using six ATP equivalents each molecule of glucose synthesised). Because metformin has a positive charge, the membrane potentials across the plasma membrane and mitochondrial inner membrane (positive outside) force metformin into the cell and then into the mitochondria, resulting in concentrations up to 1000-fold higher than in the extracellular media. [31, 32]. Metformin's suppression of Complex I of the respiratory chain, which lowers ATP generation, is the most extensively studied mitochondrial function.[7, 31]. The high extracellular concentrations (mmol/l) required to observe rapid effects have been a persistent criticism of this mechanism, though lower concentrations of metformin (50–100 mol/l) do inhibit Complex I in rat hepatoma (H4IIE) cells after several hours; this delay was ascribed to the slow uptake of metformin by mitochondria, which has recently been observed experimentally. [33]. Furthermore, other investigations have found no changes in cellular ADP: ATP ratios after metformin administration, despite the fact that they can be seen with phenformin. [34]. Concurrent inhibition of this mechanismin cells undergoing gluconeogenesis could explain the limited impact on ADP:ATP ratios. [32]. Other effects of respiratory chain inhibition besides ATP generation, such as alterations in the NAD+: NADH ratio, could possibly play a role in metformin's gluconeogenesis effects.

[35].**Metformin-induced AMPK activation:** molecular mechanisms Metformin's capacity to stimulate the cellular energy sensor AMP-activated protein kinase can potentially be explained by its inhibition of mitochondrial activity (AMPK). AMPK functions to restore energy homeostasis by switching on catabolic pathways that generate ATP while switching off cellular processes that consume ATP once activated by increases in AMP: ATP and ADP:ATP ratios (indicative of cellular energy balance being disturbed). [36]. The concept that AMPK might be involved in metformin action was appealing since it promotes a switch from cellular nutrition storage production to breakdown. In 2001, metformin was discovered to activate AMPK in rat hepatocytes and rat liver in vivo.Although high concentrations of metformin (500 mol/l) were required to see AMPK activation after a brief (1 h) treatment of cells, significant effects were seen after much longer periods of incubation with just 20 mol/l metformin, which is more in line with the drug concentrations found in the portal vein. [33, 36]. In cells harbouring an AMPK mutant that is hypersensitive to changes in AMP or ADP, neither metformin nor phenformin activated AMPK, indicating that biguanides function via raising cellular AMP: ATP/ADP:ATP ratios. However, glucose deprivation and modest doses of metformin can activate AMPK by a different mechanism involving the formation of a complex with the proteins Axin and late endosomal/lysosomal adaptor, MAPK, and mTOR activator 1 (LAMTOR1; Fig.2), the latter being a lysosomal protein.Metformin could therefore activate AMPK through a mechanism involving the lysosome rather than the mitochondrion.

[2]. **Metformin's effects on hepatic gluconeogenesis, bothAMPK-dependent and AMPK-independent** 5-aminoimidazole-4-carboxamide ribonucleoside (AICAR), a nucleoside that is taken up by cells and phosphorylated to the nucleotide 5- amino-4-imidazolecarboxamide riboside 5′-monophosphate (ZMP), which mimics all of the effects of AMP on the AMPK system, was the first pharmacological activator of AMPK to be developed. The discovery that AICAR reduced expression of the gluconeogenic enzymes PEPCK and glucose-6-phosphatase (G6Pase; Fig. 2) initially supported the theory that metformin's ability to suppress hepatic glucose synthesis was due to AMPK activation. However, additional AMP-sensitive enzymes, such as fructose-1,6-bisphosphatase, a crucial enzyme in gluconeogenesis that is allosterically inhibited by both AMP and ZMP, are similarly modulated by ZMP. In hepatocytes from control mice or mice lacking both AMPK catalytic subunits in the liver,acute treatment with metformin or AICAR suppressed glucose production equally well, while metformin acutely increased glucose tolerance in both mouse strains. Metformin increased the

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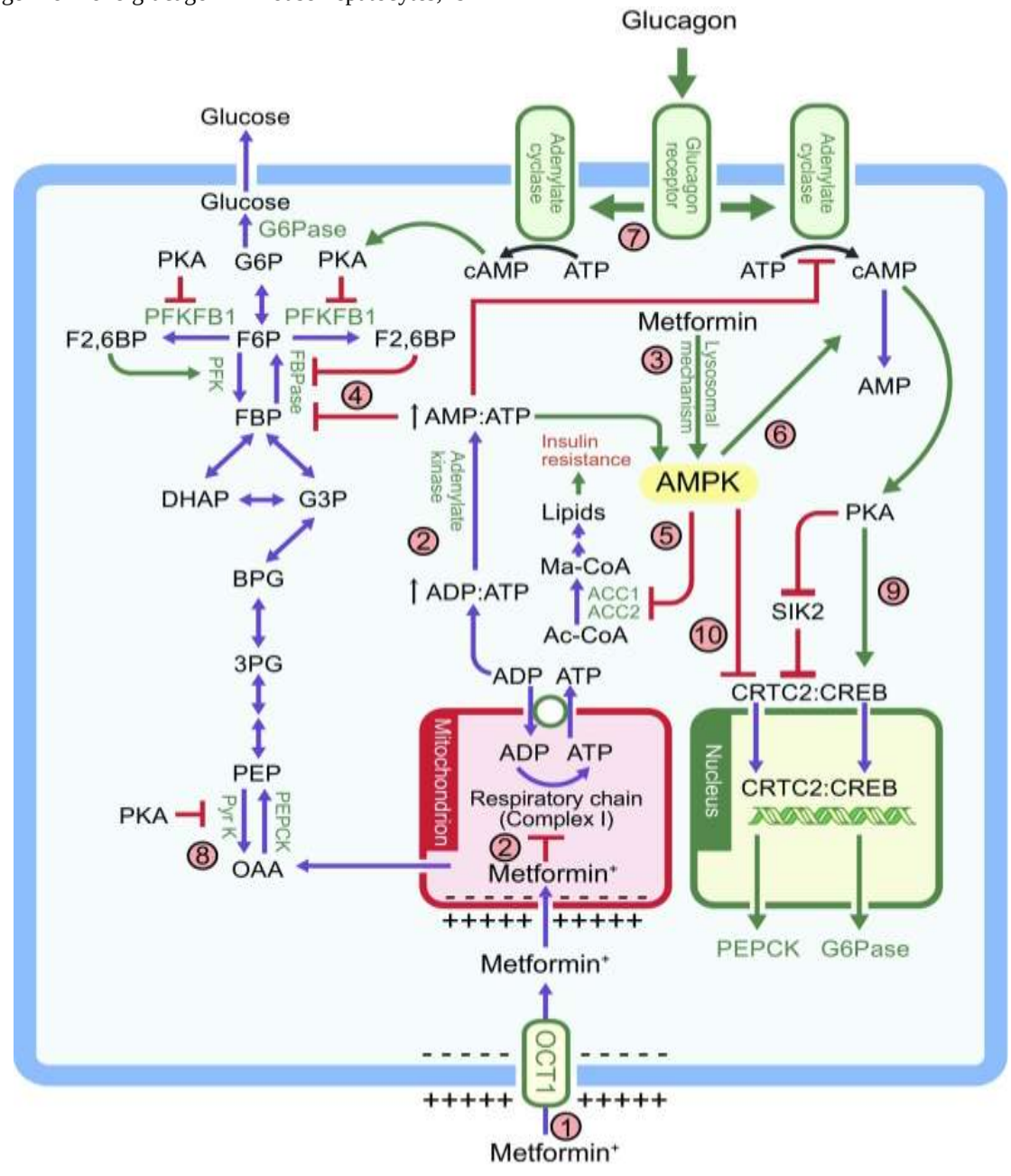
cellular AMP:ATP ratios in hepatocytes, which is consistent with respiratory chain inhibition. The rapid suppression of glucose synthesis by metformin or AICAR appears to be attributable to AMP or ZMP inhibition of fructose-1,6-bisphosphatase, respectively. AICAR and metformin, on the other hand, lowered expression of mRNAs encoding G6Pase and PEPCK in both control and AMPK-null hepatocytes. Adenylate cyclase, which creates cAMP in response to the hunger hormone glucagon in mouse hepatocytes, is (like fructose-1,6-bisphosphatase) blocked by AMP, which could explain this. As a result, AMP could have a non-AMPK effect, lowering cAMP and lowering gluconeogenic enzyme expression. Treatment of mouse hepatocytes with a more specific AMPK activator lowered glucagon-induced cAMP levels, and this was connected to direct AMPK-mediated phosphorylation of the cAMPspecific 3′,5′-cyclic phosphodiesterase 4B (PDE4B), initiating cAMP breakdown (Fig. 1).



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[2].Figure. 2Metformin influences liver metabolism through a variety of mechanisms. [37]. It's worth noting that the potential impact of metformin on mitochondrial glycerophosphate dehydrogenasehas been left out of the equation. [38]. (1) The organic cation transporter-1 catalyses the uptake of metformin into hepatocytes (OCT1). [31]. Because of the membrane potentials across the plasma membrane and the mitochondrial inner membrane, the drug accumulates in cells and, more importantly, in mitochondria.

[33]. (2) Metformin inhibits Complex I, inhibiting mitochondrial ATP synthesis and, as a result, raising cytoplasmic ADP: ATP and AMP:ATP ratios (the latter due to adenylate kinase reaction displacement); these changes activate AMPK. [36]. (3) Alternatively, AMPK can be activated through a lysosomal process, which requires Axin, a late endosomal/lysosomal adaptor, MAPK, and mTOR activator 1 but is not depicted in detail here (LAMTOR1). [39, 40]. (4) Increases in the AMP:ATP ratio reduce fructose-1,6-bisphosphatase (FBPase), which inhibits gluconeogenesis and lowers cAMP production, as well as inhibiting adenylate cyclase and lowering cAMP production. [41]. (5) Activated AMPK phosphorylates the ACC1 and ACC2 isoforms, limiting fat synthesis and instead increasing fat oxidation, lowering hepatic lipid reserves and improving insulin sensitivity. [42]. (6) AMPK also phosphorylates and activates the cAMP-specific 3′,5′-cyclic phosphodiesterase 4B (PDE4B), reducing cAMP through a different pathway. [43, 44]. (7) Glucagon-induced increases in cAMP activate cAMP-dependent protein kinase A (PKA), which causes a switch from glycolysis to gluconeogenesis via phosphorylation and inactivation of PFKFB1, resulting in a decrease in fructose-2,6-bisphosphate (F2,6BP), an allosteric activator of phosphofructokinase (PFK) and inhibitor of fructose-1 (FBPase). PKA also phosphorylates and inactivates the liver isoform of the glycolytic enzyme pyruvate kinase (Pyr K) and (9) phosphorylates the transcription factor cAMP response element binding protein (CREB), triggering transcription of the PEPCK and G6Pase genes. (10) Phosphorylation of CREB-regulated transcriptional co-activator-2 (CRTC2) by AMPK or AMPK-related kinases like salt-inducible kinase 2 (SIK2) causes CRTC2 to be maintained in the cytoplasm, counteracting PKA's effects on PEPCK and G6Pase transcription. [44]. SIK2 is inhibited by PKA through numerous phosphorylation sites.

V.2 ANTICANCER ACTION OF METFORMIN:

[45]. In 2005, a study linked metformin use to a lower risk of cancer, catapulting the medicine into the spotlight of cancer research. Diabetes has been linked to a 1.2–2.0-fold increase in the risk of cancer. [4]. Metformin, according to a 2010 study, reduces this risk by about 40% when compared to other antidiabetic medications. [46, 47]. Several studies have found that there is a significant reduction in the risk of all-cause and cancer-specific death, as well as a slowing of cancer progression. [45, 48, 49]. However, a population-based study found no link between metformin use and better survival in diabetes patients with breast cancer aged >65 years, which was consistent with the findings of several other investigations.

Little is known about the cancer-related effect of metformin in nondiabetic patients. The interaction between the patient's metabolic profile and the tumour’s molecular features adds to the complication of metformin's effects on tumorigenesis, which are likely both systemic (indirect) and local (direct) (Figure 2, 3).

SYSTEMIC EFFECT OF METFORMIN ON TUMOURIGENESIS:

[50]. Hyperinsulinemia has been linked to a poor prognosis in a number of malignancies (including breast, colon and prostate cancer).Metformin decreases systemic glucose levels and improves secondary hyperinsulinemia in patients with insulin resistance, reducing the latter's impact on tumour growth and progression. Metformin can damage insulin-sensitive neoplastic tissues indirectly as a result of this activity, without having to accumulate in cancer cells. Our knowledge of this principle is still restricted. [51]. Although exogenous insulin used to treat diabetes does not cause cancer, there is some debate about the risk of cancer in people taking the long-acting insulin analogue glargine. [40]. It's also probable that metformin affects other hormones, cytokines, and metabolic intermediates that promote tumorigenesis. It's worth looking into a systemic effect linked to diminished glucagon signalling in glucagon-responsive cells. More research is needed in patients withnormoglycemia to fully understand this concept.

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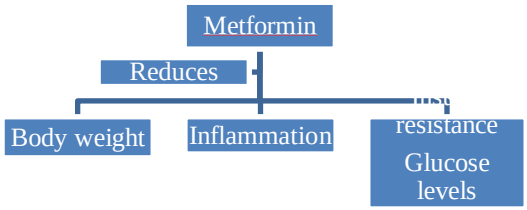

Figure. 3 Systemic effect of metformin on tumorigenesis.

DIRECT EFFECT OF METFORMIN IN CANCER

AMPK-DEPENDENT ACTION OF METFORMIN IN CANCER:

[16, 52]. The inhibition of the mammalian target of rapamycin (mTOR) pathway by LKB1 and AMPK is perhaps metformin's most significant anticancer impact (Figure 3). Inhibition of mTOR impairs protein synthesis and, as a result, tumour cell proliferation. LKB1 loss is common in cancer, and a germline LKB1 mutation causes Peutz–Jeghers syndrome, a cancer-predisposing condition.

[16]. mTOR is a catalytic subunit of the mTORC1 and mTORC2 multiprotein complexes. These complexes play a key role in cellular growth regulation, integrating information from a variety of hormonal signalling and energy-sensing pathways, including insulin, insulin-like growth factor 1 (IGF-1), IGF-2, and AMPK (Figure 3).

[53]. The activation of the tumour suppressor genes tuberous sclerosis complex 1 (TSC1) and TSC2, which form a mTOR-inhibiting complex, results in AMPK-dependent downregulation of mTORC1. Furthermore, AMPK suppresses RAPTOR, a positive regulator of mTOR, directly.

[54]. Metformin inhibits IGF-1–insulin signalling by phosphorylating IRS-1, which carries signals from the insulin and IGF-1 receptors to the PI3K–AKT pathway, in an AMPK-dependent manner (Figure 3). This activity has the ability to suppress mTOR signalling as well. [55]. During chronic metformin exposure, however, various regulatory feedback loops may neutralise this cascade's antitumor effect. [56]. p53, a tumour suppressor protein, regulates a number of genes that block the AKT and mTORC1 pathways.Although p53 is one of AMPK's targets (Figure 3), the significance of metformin in p53 activation is debatable.

[57]. Metformin also increases the expression of DICER1, an enzyme involved in microRNA production. Loss of function mutations in DICER1 cause a complicated tumour phenotype, suggesting that metformin-induced DICER1 expression could be another anticancer strategy (Figure 3).Metformin inhibits the proto-oncogene c-MYC as well as hypoxia-inducible factor 1 (HIF-1) through the AMPK pathway (Figure 3). Importantly, AMPK and HIF-1 play an important role in cancer metabolic change.

[16, 58]. Even under aerobic settings, rapidly dividing cells, such as tumour or inflammatory cells, have altered metabolism that favours glycolysis over oxidative phosphorylation as an energy source, a phenomenon known as the Warburg effect. The availability of intermediates as building blocks for proliferating cells is ensured by this metabolic transition, which stimulates fatty acid production. [59]. The mTORC1-activated HIF-1, a transcription factor that promotes the production of glycolytic enzymes, GLUT-1, and monocarboxylate transporter 4 (MCT4), which is involved in lactic acid transport, is likely one of the primary mediators of this reprogramming.

[60]. Because a deficiency in the LKB1–AMPK pathway increases the chance of pre-neoplastic cells metabolically transforming, many tumours have inactive LKB1. [61]. In vivo, AMPK has been demonstrated to inhibit the Warburg effect and tumour growth. [57]. Metformin reduced HIF-1 alpha mRNA and protein levels in a breast cancer model, indicating anti-proliferative and anti-Warburg activity, most likely through AMPK. [62, 63]. Metformin also performed anti-mitotically in colon cancercells by decreasing fatty acid synthaseproduction and favouring fatty acid oxidation.

[64]. Metformin's impact on cell metabolism and tumour growth is debatable. Metformin can reverse the Warburg effect in pre-neoplastic cells with an intact AMPK axis (that is, inhibit oxidative glycolysis). [16]. The presence of LKB1 and AMPK in developed tumours, as opposed to pre-neoplastic cells, may give a survival

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benefit to cancer cells by protecting them from energy stress.

[65]. Under specific microenvironments, such as acidic pH,it might even produce an increase in glycolytic flux; hence, AMPK activators may be hazardous. [19]. In contrast, the absence of LKB1 or AMPK in existing tumours makes cancer cells more susceptible to metformin-induced ATP depletion because their ability to restore energy balance is reduced.

AMPK-INDEPENDENT METFORMIN EFFECTS IN CANCER:

[66, 67]. While growth factors control mTORC1 via the PI3K–AKT–TSC1–TSC2 axis, amino acids can activate mTORC1 signalling independently of AMPK via the RAG family of GTPases (also known as the Ras-related GTPases). [68]. The RAG GTPases attract mTORC1 to the lysosomal surface, where it is activated by RHEB, after it is activated by the Regulatory complex. Metformin blocks mTORC1 signalling by inactivating the Regulatory complex, simulating the effect of amino acid deficiency. [16, 67]. This mechanism of action, which is sensitive to changes in energy status, could be useful in the treatment of specific cancers and, in conjunction with dietary energy restriction, in cancer prevention.

[70]. Metformin decreases the generation of reactive oxygen species, oxidative stress, and DNA damage by inhibiting mitochondrial complex I, lowering the risk of mutagenesis. [69]. The existence of common genetic variations near the ataxia telangiectasia mutated (ATM) gene locus has been linked to variation in the glycaemic response to metformin in patients with type 2 diabetes mellitus. [31]. This finding suggests that ATM activation is involved in metformin-dependent signalling. ATM is a tumour suppressor protein that is part of the DNA-damage response network system, which is necessary for DNA repair and cell cycle control. Ataxia telangiectasia is a neurological disorder linked to a higher risk of cancer, insulin resistance, and type 2 diabetes mellitus. The ATM-mediated reparatory impact is likely to involve both AMPK-dependent and AMPK-independent pathways.

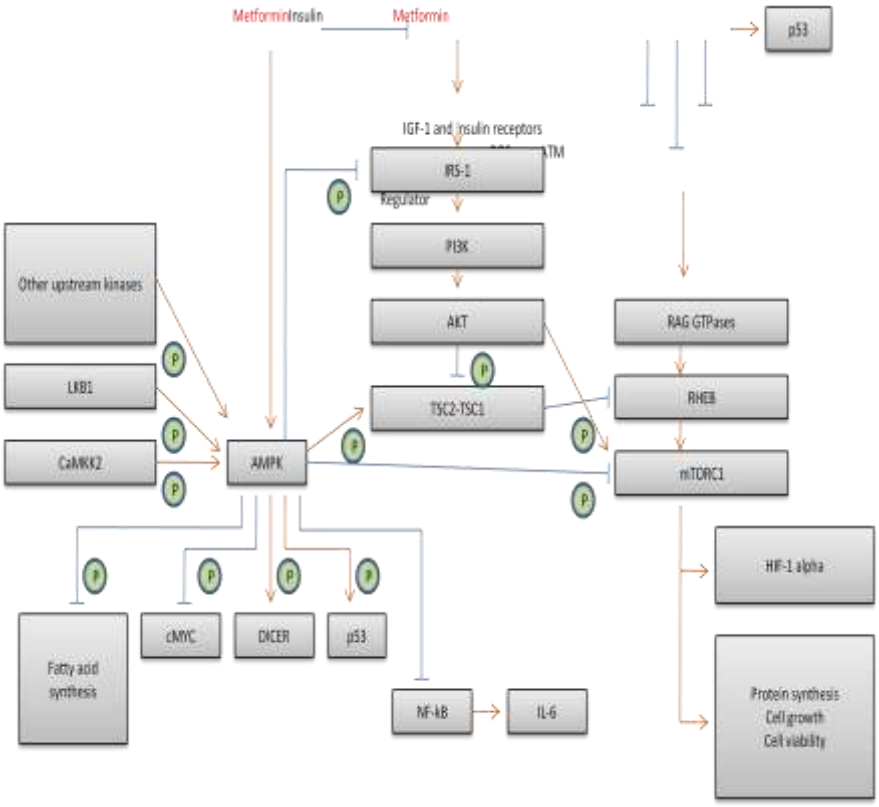

Figure. 4Direct effects of metformin in cancer

VI. APPLICATION OF METFORMIN IN DERMATOLOGY:

Drug has shown efficacy and therapeutic applications in dermatological disorders too.

VI.1 ACANTHOSIS NIGRICANS

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[71]. Acanthosis nigricans (AN) is a common cutaneous disorder marked by black, coarse, thicker skin that feels velvety. The neck, axilla, antecubital and popliteal fossa's, groyne folds, and infrequently additional places such as the face, eyelids, umbilical area, knuckles, palms, soles, nipple, and areola are all affected. [72].The link between benign AN and insulin resistance and hyperinsulinemia has recently been identified, with obesity being a common complication in these patients. In addition, insulin levels in obese AN patients were shown to be considerably greater than in obese people who did not have AN.

MECHANISM OF ACTION:

The activation of receptors belonging to the tyrosine kinase family is involved in the development of AN. A defect in the translocation of glucose transporter 4 (GLUT 4) to the plasma membrane of adipocytes and myocytes enhances the activation of insulin-like growth factor receptors (IGF-R). Metformin reduces hyperinsulinemia by inhibiting GLUT 4, which improves AN. Combination therapy of thiazolidines or glimepiride with metformin would be worth considering in resistant cases of AN.

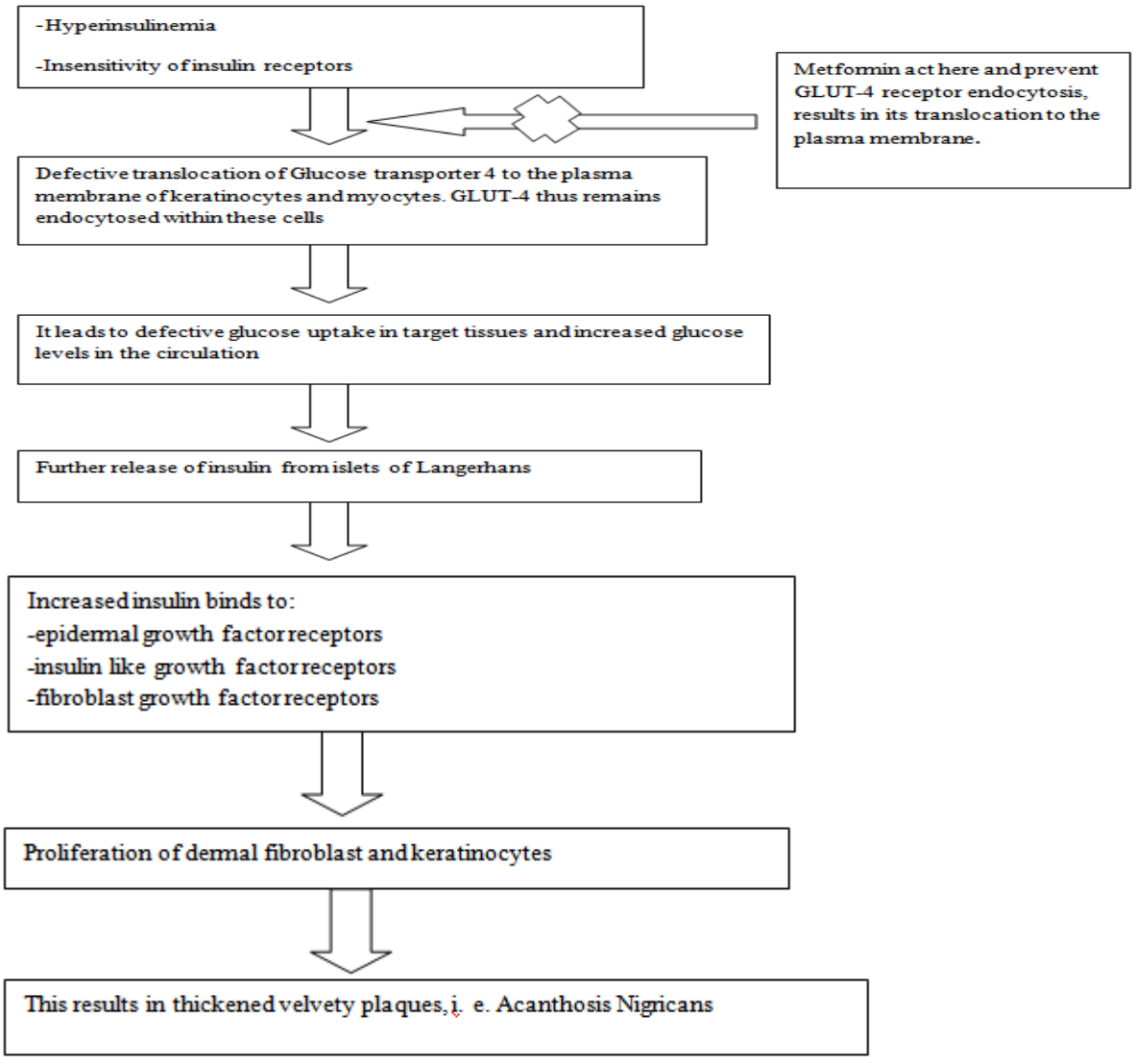

Figure. 4 Mechanism of action of metformin in Acanthosis Nigricans

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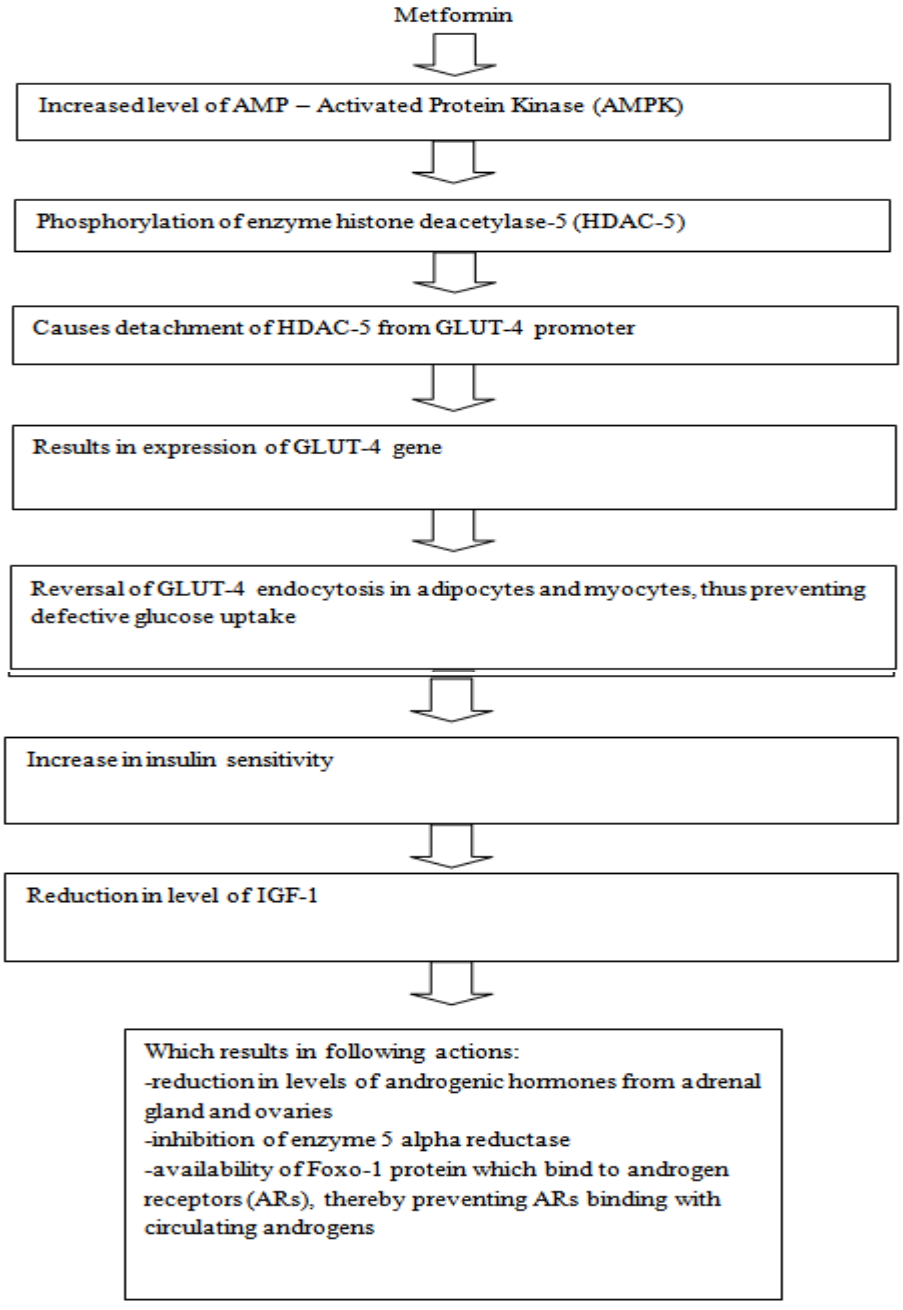
VI.2 ACNE

[73]. Acne is an inflammatory condition that affects the follicles of the pilosebaceous glands. In a large number of acne sufferers, hyperandrogenism has been discovered to be a key contributory cause. IGF-1 levels have been found to be higher in both males and females with acne. Furthermore, in postadolescent acne patients, a direct link between serum IGF-1 levels and mean facial sebum excretion rate has been reported. Dihydrotestosterone and dehydroepiandrosterone sulphate levels in the blood were also linked to IGF-1 levels. To elaborate, IGF-1 is highly expressed in sebocytes and suprabasal cells of the sebaceous ducts in the human body, while IGF-R is widely expressed throughout the sebaceous glands.

MECHANISM OF ACTION:

[74, 75, 76]. Metformin has been discovered to play a role in hormonal acne. Figure 5. depicts the exact mechanism of metformin in this regard.

Metformin



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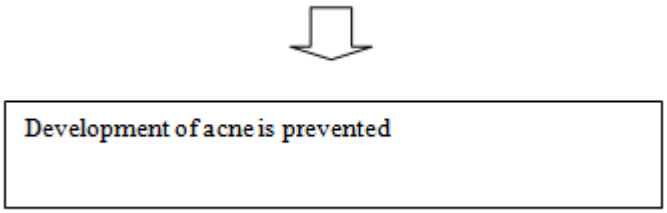


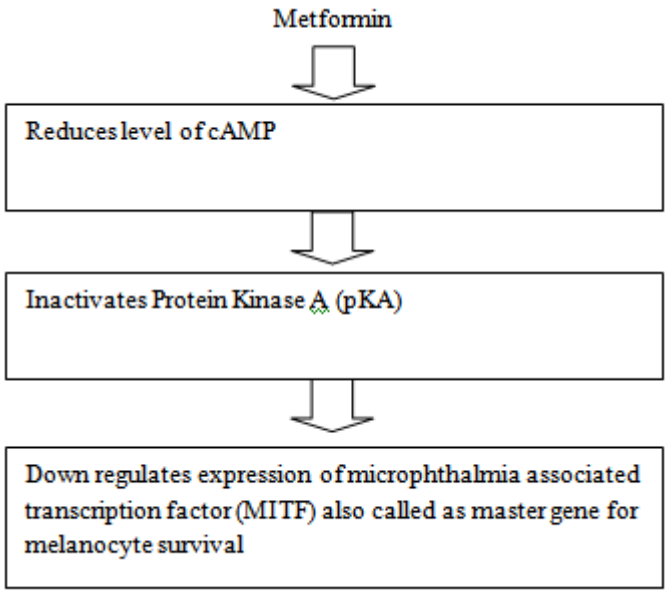
Figure. 5Mechanism of action of metformin in Acne

VI.2 HYPERPIGMENTATION

[18, 77]. Metformin's involvement in the treatment of hyperpigmentary diseases has only recently been clarified. Though these proofs are currently based on animal studies, this anti-diabetic medicine could be used for this indication in people very soon. Various molecular processes have been linked to metformin's therapeutic effects. [77]. Metformin inhibits the expression of three melanogenic proteins: tyrosinase, tyrosine-related protein (TRP)-1, and tyrosine-related protein (TRP)-2. [78]. Metformin causes this via lowering the amounts of cyclic adenosine monophosphate, which inhibits the activation of protein kinase A. As a result, the expression of the microphthalmia-associated transcription factor is reduced (MITF). MITF is a critical transcription factor that has been dubbed the "master gene" for the survival of melanocytes. When its activity is inhibited, transcription of numerous melanogenic proteins such as tyrosinase, TRP-1, TRP-2, MART-1, and protein kinase C-beta (PKC-beta) is inhibited. [18]. PKC- activity is also inhibited by metformin. PKC- normally binds to melanosomes and phosphorylates tyrosinase after being activated by diacylglycerol (DAG), so increasing melanogenesis. Metformin prevents the activation of PKC-beta provided by DAG.

[79]. However, this effect has only been observed with topical metformin, not with systemic administration of the medication. After crushing metformin tablets to make a 30% weight-to-volume solution in a standard vehicle containing 70% alcohol and propylene glycol, the topical treatment was created. After that, the solution was administered to the tails of experimental animals for an 8-week period. Metformin's role in hyperpigmentary cutaneous disorders was proven using a topical formulation.

MECHANISM OF ACTION:



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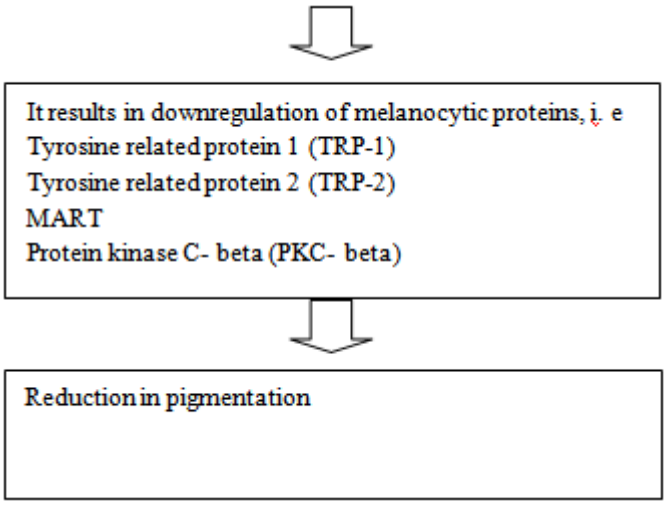

Figure. 6 Mechanism of action of metformin in Hyperpigmentation

VI.3 ERUPTIVE XANTHOMAS

[1]. Eruptive xanthomas (EXs) are subcutaneous lipid deposits that appear as tiny yellow papules with a diameter of 2 to 5 mm. They're frequently linked to dyslipidaemia types I, VI, and V. Metformin works in EXs by activating adenosine monophosphate-activated protein kinase (AMPK) in hepatocytes, which reduces the activity of acetyl-CoA carboxylase, resulting in fatty acid oxidation and reduced expression of lipogenic enzymes, which is responsible for metformin's beneficial effect in this indication. A successful case of EX resolution in a 65-year-old man with type 2 diabetes who was using metformin has been published.

VI. 4 MELANOMA

[80]. Metformin stimulates the p53 tumour suppressor gene, which activates AMPK and causes anti-cancer signalling in melanoma. [81]. Metformin also inhibits the transcription factors Snail and Slug, stops the epithelial-mesenchymal transition in melanoma, and lowers matrix metalloproteinase activity, boosting anti-invasive and antimetastatic actions. Martin et al. have revealed that metformin can accelerate the proliferation of BRAF^V600E mutant melanoma cells in vitro by upregulating vascular endothelial growth factor (VEGF). The development of these malignant cells was inhibited in vivo when metformin was coupled with VEGF inhibitors. As a result of these findings, it may be prudent to assume that combining BRAF mutant melanoma resistant to BRAF inhibitors with metformin and VEGF antagonists may be a viable alternative.

VII. ADVERSE EFFECTS

CUTANEOUS:

[82]. A case of bullous pemphigoid emerging after the use of metformin in a patient who was also on gliptins has been reported. However, it was unclear whether metformin was to blame for the dermatoses in this case. [49]. Azzam et al. described metformin-induced lichen planus in a case report. [83]. Metformin has been linked to the development of leukocytoclastic vasculitis in a number of studies.

NONCUTANEOUS:

These include: -

Flatulence, indigestion, myalgia, nausea, vomiting, diarrhoea, heartburn, palpitations, light headedness, dyspnea, lactic acidosis, and flu-like symptoms.

VIII. DRUG INTERACTIONS

[84]. Metformin, as a strong base, is a cation at physiological pH. As a result, transporters include organic cation transporters, multidrug and toxin extruders, and plasma membrane monoamine transporters have a role in Metformin absorption, distribution, and excretion. [24]. Metformin oral absorption and hepatic uptake are mediated by organic cation transporters-1 and -3, while Metformin renal excretion is mostly mediated by Metformin transporters such as multidrug and toxin extruders-1 and 2-k, as well as organic cation transporter 2. [85]. Inhibitors of Metformin transporters may reduce Metformin clearance and raise its plasma concentrations, increasing the risk of Metformin-associated lactic acidosis.

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[86]. Metformin is unlikely to be implicated in many drug–drug interactions because it is not metabolised. Metformin-related clinically relevant medication interactions are thus uncommon. [86, 87]. Some cationic medicines that are removed via renal tubular secretion, such as amiloride, digoxin, morphine, procainamide, quinidine, quinine, ranitidine, triamterene, trimethoprim, and vancomycin, may compete with metformin for removal. Cimetidine, furosemide, or nifedipine may enhance the concentration of metformin if used together.

[84]. Cimetidine, contrast agents, dolutegravir, phenprocoumon, pyrimethamine, ranolazine, rifampicin, St John's wort, trimethoprim, vandetanib, and verapamil are among the medications that interact with metformin, however only a small number of clinically significant drugs have been identified (Table 2). [88]. Verapamil significantly reduces metformin's glucose-lowering efficacy while having no influence on its pharmacokinetics. This is most likely due to organic cation transporter 1 being inhibited competitively. [86]. Metformin should be stopped at least 48 hours before administering iodinated contrast media, which can cause acute renal failure, and only resumed if renal function is normal. [89]. Metformin reduces the anticoagulant action of phenprocoumon, according to a study.

[82]. Table 2 Clinically significant pharmacokinetic drug interaction of metformin.

MEDICATION	MECHANISM OF INTERACTION	CONSEQUENCES/EFFECTS	RECOMMO NDATIONS
Cimetidine	Elimination It competes with metformin for renal elimination and decreases the excretion of metformin.	It increases exposure of Metformin and risk of Metformin associated lactic acidosis.	It is recommended to reduce the dose of Metformin when Cimetidine is co-prescribed.
Trimethoprim	It inhibits Metformin elimination moderately through the inhibition of OCTs and MATEs.	It decreases Metformin clearance and increases plasma concentration.	Monitor carefully in patients with renal dysfunction or patients taking higher doses of Metformin
Rifampin	Absorption The mechanism may involve rifampinmediated induction of the OCT1 in the gastrointestinal tract.	Rifampin may increase the gastrointestinal absorption and therapeutic efficacy of metformin.	Close clinical monitoring of glycaemic control is recommended, and the dosage of metformin may be adjusted as necessary.
Dolutegravir	It is an inhibitor of both OCT2 and MATE1 transporters within the renal tubules.	It may increase the risk of hypoglycaemia and GI intolerance due to increased plasma concentrations of Metformin.	Prescribers may adjust the Metformin dose to prevent intolerable adverse effects

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			while prescribing both drugs.
Pyrimethamine	Elimination It decreases renal clearance of Metformin by the inhibition of OCT2 and MATE transporters.	Co-administration of Pyrimethamine with Metformin results in elevated plasma concentrations Metformin.	Metformin dose adjustment should be considered
Ranolazine	Elimination It may decrease the Metformin elimination through the inhibition of OCT2 transporter.	The plasma concentration of Metformin is elevated by the co-administration of Ranolazine.	This interaction is dose dependent and it is recommended that the daily dose of Metformin should not exceed 1700 mg in patients taking Ranolazine 1000 mg two times daily.
Vandetanib	Elimination Vandetanib is a potent inhibitor of MATE1 and MATE2K transporters.	Its co-administration with Metformin may result in increased plasma concentration of Metformin due to decreased elimination.	The patients receiving both drugs should be monitored carefully for Metformin toxicity.

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