Review

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Exploring the Next Generation of Metformin Derivatives and Their Biomedical Promise

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Abstract: Metformin is a drug recommended as the first-line agent for the treatment of patients with type 2 diabetes mellitus due to its high efficiency and good safety profile. Additionally, literature has described its favourable effect in treating several other diagnoses. This review aims to summarize recent research on metformin modification and derivatization, which has led to agents with higher efficiency or expanded the application possibilities of metformin. Namely, buformin, phenformin, imeglimin, lixumistat, IM176 derivatives, moroxydine, proguanil, cycloguanil, metformin sulfenamides and sulphonamides, polypeptide derivative LysMET, artesinate-metformin conjugate AM2. Additionally, salts such as metformin hydrochloride, metformin hydrobromide, metformin hydroiodide, metformin acetate, metformin embonate, metformin threonate, metformin tartrate, metformin citrate, metformin mesylate and metformin maleate. The goal is to highlight recent research efforts and introduce perspectives for novel and effective biomedical substances within the still unexplored field.

Keywords: metformin; biguanide; metformin derivatives; structural modification; medicinal chemistry; diabetes mellitus

1. Introduction

Metformin (Fig. 1), also known as 3-(diaminomethylidene)-1,1-dimethylguanidine (IUPAC name) or 1,1-Dimethylbiguanide or N,N-dimethylimidodicarbonimidic diamide is a member of the class of guanidines – a biguanide carrying two methyl substituents at position 1.

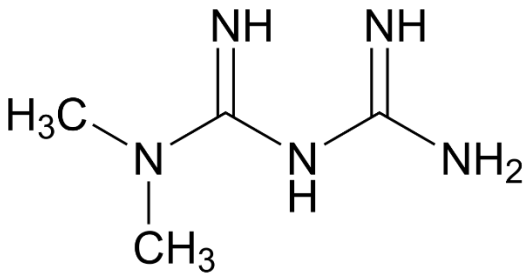

Figure 1. Metformin structural formula.

Metformin is primarily an antihyperglycemic agent and a first-line pharmacotherapy used in the management of type 2 diabetes mellitus, because it lowers blood glucose concentrations without causing hypoglycemia. Metformin inhibits the mitochondrial respiratory chain in the liver, leading to activation of AMP-activated protein kinase, enhancing insulin sensitivity for type 2 diabetes mellitus. The discovery of metformin traces back to medieval times when the use of *Galega officinalis*, a perennial herbaceous plant, in traditional herbal medicine was associated with treating symptoms of what is now known as type 2 diabetes mellitus. Other names for *Galega officinalis* include goat's rue, French lilac, Spanish sainfoin, Italian fitch, or false indigo. Traditionally, goat's rue was used for expelling parasites and treating snakebites. It is believed to have served as a diuretic and tonic in typhoid conditions and as a stimulant for the nervous system. It also exhibits fever-reducing effects.

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However, metformin provides also other medical benefits. Metformin is known to cause weight loss as a favourable side effect. Unfavourable side effects are mainly lactic acidosis, digestive problems, such as diarrhoea, vomiting, and flatulence. Common side effects are also abdominal discomfort, headaches and lack of energy. Alternatives of metformin are for example Dipeptidyl peptidase 4 (DPP-4) inhibitors. These medications offer the potential to enhance A1C scores without inducing hypoglycemia. Their mechanism involves inhibiting the enzyme DPP-4, thus preventing the degradation of glucagon-like peptide 1 (GLP-1) and gastric inhibitory peptide (GIP). GLP-1 and GIP are innate hormones that aid in lowering blood glucose levels. By prolonging the activity of these hormones, DPP-4 inhibitors facilitate glucose regulation. Generally, DPP-4 inhibitors are well tolerated. Other options are GLP-1 and dual GLP-1/GIP receptor agonists. Both GLP-1 and GIP are endogenous hormones crucial for glucose regulation. These medications mimic the actions of these natural hormones but possess resistance to degradation by DPP-4. Consequently, they facilitate blood glucose reduction and may additionally contribute to weight loss and the prevention of heart disease. Other possibilities are Sodium-glucose cotransporter 2 (SGLT2) inhibitors. Glucose present in the bloodstream undergoes filtration in the kidneys, where it's either excreted in urine or reabsorbed into the blood. SGLT2 plays a role in the reabsorption of glucose in the kidneys. Consequently, SGLT2 inhibitors impede this process, facilitating the elimination of surplus glucose through urine. These medications offer the potential to enhance blood glucose control, promote weight loss, and reduce blood pressure. They may be prescribed by a physician for individuals with type 2 diabetes mellitus (T2DM) who also experience heart or kidney issues. However, it's important to note that they may elevate the risk of genital yeast infections. Next availability are Sulfonylureas. These medications function by promoting the release of insulin from the beta cells in the pancreas. While all sulfonylurea drugs have comparable impacts on blood sugar levels, they vary in terms of side effects, interactions with other drugs, and dosing frequency. Common side effects may encompass hypoglycemia and weight gain. Last option are Thiazolidinediones (TZDs). These medications enhance the effectiveness of insulin in muscle and fat tissues while simultaneously decreasing glucose production in the liver. TZDs are associated with a reduced likelihood of hypoglycemia. However, individuals using drugs from this class may face an elevated risk of heart failure, and they may also experience fluid retention in the lower extremities.

Preclinical studies show that metformin has been identified as a potentially efficacious antitumor agent that acts collaboratively with other immunotherapeutic agents involved in tumor elimination [1]. Metformin is also effective in treating several skin diseases, including acne vulgaris, hidradenitis suppurativa, psoriasis and hirsutism [2], and is used to treat inflammatory diseases, endocrine-related dermatosis, and hyperpigmentation illnesses [3]. According to Feng [4], metformin can improve the dysfunction of macrophages that causes accelerated atherosclerosis. As observed by Hammad Uddin [5] it showed also osteogenic, regenerative, anti-neoplastic and osseointegration properties in dentistry. Metformin is also classified as an antimicrobial agent [6]. The antibacterial activity was studied against two highly resistant strains of Gram-positive and Gram-negative bacteria, namely methicillin-resistant *Staphylococcus aureus* and multidrug resistant *Pseudomonas aeruginosa*. It was found that metformin was able to reduce the resistance of these two strains to the tested antibiotics namely, doxycycline, levofloxacin, ampicillin, chloramphenicol, and rifampicin. Furthermore, these combinations (metformin-tested antibiotics) provided either a synergistic or an additive effect; suggesting that metformin efficiently enhances and potentiates the activity of these antibiotics. Metformin is also effective in treating osteoarthritis [7,8], neurological disorders [9], inflammation [10], endometriosis [11], epilepsy [12], vascular disease [13], kidney disease [14], renal diseases [15], preeclampsia [16], multiple sclerosis [17], musculoskeletal disorders [18], retinal diseases [19] and venous thrombosis [20]. Obtained data also suggest its effectiveness in targeting several age-related morbidities in humans [21,22]. Metformin is also very efficient in case of polycystic ovarian syndrome (PCOS) treatment. Typically, it impacts approximately 5 to 10% of the population, with ultrasound techniques easily revealing a range of cysts of various sizes in both ovaries. PCOS is strongly linked to a hyperglycemic condition, often tied to insulin resistance and type 2 diabetes. In PCOS patients, there is typically a consistent basal insulin secretion, leading to a

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state of hyperinsulinemia and consequently, relative dysfunction of pancreatic β-cells. Furthermore, metformin is expected to have an anticoagulant effect. However, its therapeutic use as an anticoagulant agent has not yet been approved, and further analysis is required before it can be fully endorsed.

There are various patented procedures for metformin synthesis which differ in reaction conditions and purification strategy, but almost all involve reacting the hydrochloride salt of dimethylamine with cyanoguanidine. First, the dimethylamine hydrochloride is deprotonated by cyanoguanidine, forming a guanidinium cation. The dimethylamine nitrogen now has a free lone pair available for nucleophilic attack at the electrophilic nitrile carbon. Consequently, a proton transfer gives the metformin HCl salt. Reaction scheme of metformin synthesis is introduced in following Figure 2.

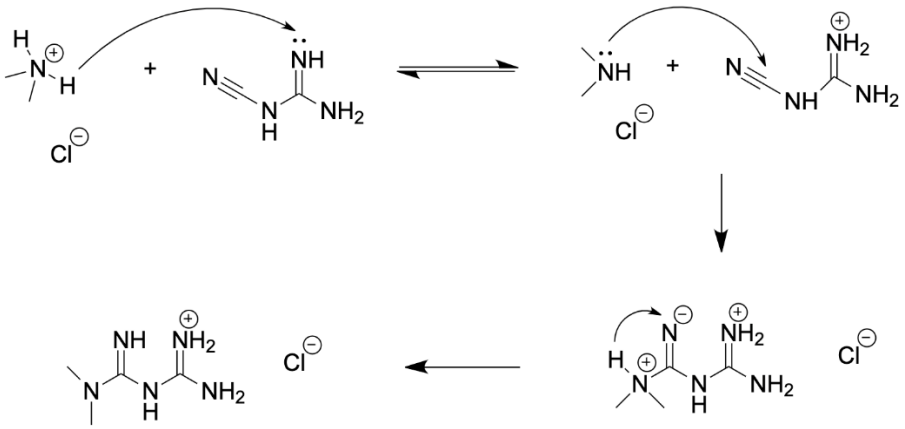

Figure 2. Scheme of metformin synthesis.

Several clinical trials show that metformin inhibits tumor growth, invasion, and metastasis [23,24]. It is used in monotherapy or in combination with various chemotherapeutic or immunotherapeutic agents [25]. For example, In the context of head and neck squamous cell carcinoma, metformin has been studied in combination with chemoradiotherapy and has demonstrated promising results. It was found that combining metformin with chemoradiotherapy resulted in high overall survival rates for patients with head and neck squamous cell carcinoma. Metformin is also known to enhance the effects of immune checkpoint inhibitors and other chemotherapeutic agents. Its ability to improve the immune response by increasing NK cell activity and inhibiting cancer-promoting pathways like CXCL1 suggests that it can synergize with other drugs to improve outcomes. The advantageous role of metformin was observed in cancer treatment for malignant skin tumors [2], bone cancer [26], breast cancer [27], head and neck squamous cell carcinoma [28], esophageal squamous cell carcinoma [29], glioblastoma [30], small cell lung cancer [31], non-small cell lung cancer [32,33], lung adenocarcinoma [34], endometrial cancer [35], ovarian cancer [36], urothelial cancer [37], prostate cancer [38], colorectal cancer [39], pancreatic cancer [40], hepatocellular carcinoma [41], multiple myeloma [42], acute lymphoblastic leukemia [43] etc. However, despite all these findings, there are also numerous papers suggesting that there is no evidence for a decreased risk of various cancer types in association with metformin use [44–47]. There are proposed various mechanisms by which metformin exerts anticancer effect. Metformin inhibits oxidative respiration by acting on complex I of the mitochondrial respiratory chain, thus inhibiting the synthesis of ATP, increasing the adenosine diphosphate (ADP)/ATP ratio and adenosine monophosphate (AMP)/ATP ratio, and promoting the activation of AMPK. In addition, studies have shown that metformin-induced glucose starvation can also lead to the activation of AMPK through the lysosomal v-ATPase-Regulator complex. AMPK is a key signal integration factor crucial for the control of mitochondrial health and metabolism and is also closely related to cell senescence and cell fate [48]. The potential anticancer impact of metformin might not solely rely on AMPK activation.

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Research suggests an alternative mechanism wherein metformin could hinder cell DNA damage by suppressing reactive oxygen species production. Even in the absence of AMPK activity, metformin can influence AKT/mTOR signaling by directly impeding mTORC1 signaling. Moreover, metformin demonstrates the ability to restrain cyclin D1, a pivotal regulator governing the cell cycle [49]. Additionally, metformin can contribute to its anticancer properties by modulating the immune microenvironment and bolstering the immune response against cancerous cells.

The above-mentioned studies indicate a wide range of possible metformin applications, but novel advanced synthesized metformin derivatives could be more effective for treating each given disease and beneficial for the patient's comfort. Moreover, preparation of novel metformin derivatives which diminish the secondary side effect of lactic acidosis is of equal importance. Therefore, the author presents all currently available data on the studied subject, revealing significant opportunities for future research in terms of novel derivatization strategies.

2. Metformin derivates

Over the past few years, several metformin derivatives (Fig. 3) have been extensively studied. These include buformin, phenformin, imeglimin, lixumistat, IM176 derivatives, moroxydine, proguanil, cycloguanil, metformin sulfenamides and sulphonamides, polypeptide derivative LysMET, artesinate-metformin conjugate AM2. Additionally, salts such as metformin hydrochloride, metformin hydrobromide, metformin hydroiodide, metformin acetate, metformin embonate, metformin threonate, metformin tartrate, metformin citrate, metformin mesylate and metformin maleate have also been studied.

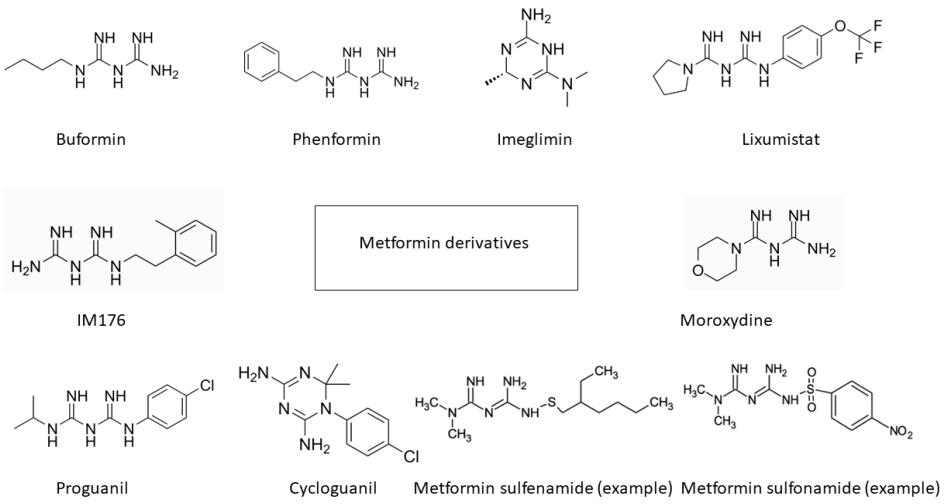

Figure 3. Metformin derivatives structures.

2.1. Buformin

Buformin, also called Butformin, 1-butylbiguanide, n-butylbiguanide, butyldiguanide or 2-butyl-1-(diaminomethylidene)guanidine (IUPAC name) is an anti-diabetic drug belonging to the biguanide class, chemically related to metformin. Buformin is a potent AMPK activator which acts as an orally active biguanide antidiabetic agent. Buformin decreases hepatic gluconeogenesis and lowers blood glucose production in vivo. Buformin also has anti-cancer activities It was withdrawn from the market in most countries due to its high risk of causing lactic acidosis. Recent studies have shown that buformin has tumor hypoxia depression capacity and exhibits potent antitumor activity in many malignant tumors [50].

2.2. Phenformin

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Phenformin or N-Phenethylbiguanide or 1-(diaminomethylidene)-2-(2-phenylethyl)guanidine (IUPAC name) is an older biguanide antidiabetic drug that was used in the past but has been largely discontinued due to its increased risk of lactic acidosis, a serious side effect. Phenformin (1-phenethylbiguanide) is an orally active antidiabetic and anticancer agent. Phenformin acts through acting APMK activation and blocking mTOR pathway. Phenformin is also a substrate of P-glycoprotein (P-gp), and an OXPHOS inhibitor. Phenformin induces cancer cell apoptosis. Metformin replaced phenformin as the preferred choice for diabetes treatment because it has a lower risk of this adverse effect. However, phenformin has been recognized as a drug possessing anti-cancer potential due to its anti-proliferative effect [51]. This was confirmed for lung cancer [52], liver cancer [53], breast cancer [54], squamous cell carcinoma [55] and malignant glioma [56]. According to Liu, phenformin, but not metformin, can efficiently suppress the inflammatory response induced by 12-O-tetradecanoylphorbol-13-acetate (TPA) in the skin. Inflammatory responses are mainly mediated by cytokines that are expressed by different types of cells, including immune cells, dermal fibroblasts and keratinocytes in the skin [57]. Furthermore, phenformin has been shown to be a more potent mitochondrial inhibitor than metformin [58].

2.3. Imeglimin

Imeglimin or (4R)-6-N,6-N,4-trimethyl-1,4-dihydro-1,3,5-triazine-2,6-diamine (IUPAC name) a recently approved drug and the first in a new class (novel mode of action) of type 2 diabetes mellitus medicines. Although not a biguanide, imeglimin shares a chemical moiety with metformin and also modulates mitochondrial complex I activity, a potential mechanism for metformin-mediated lactate accumulation. Imeglimin is an oral glucose-lowering agent. Imeglimin improves insulin sensitivity. Imeglimin also reduces reactive oxygen species production, increases mitochondrial DNA and improves mitochondrial function. The free form of the compound is prone to instability, it is advisable to consider the stable salt form Imeglimin hydrochloride that retains the same biological activity. Imeglimin improves pancreatic β-cell function and enhances insulin action in the liver and skeletal muscle [59]. Imeglimin also reduces the production of reactive oxygen species that are harmful to the human body and improves the function of mitochondria and the endoplasmic reticulum, important in the synthesis, folding, modification, and transport of proteins [60]. The safety profile of imeglimin seems to be very promising, despite long-term studies still being incomplete [61]. A recent study by Hozumi reveals that imeglimin exerts biochemical effects similar to those of metformin on mitochondrial respiration, AMPK activity, and gene expression in hepatocytes at relatively high concentrations. However, effects on the expression of certain genes related to mitochondrial function differed between the two drugs [62].

2.4. Lixumistat

Lixumistat, IM156, HL156A, HL271 or N'-[N'-[4-(trifluoromethoxy)phenyl]carbamimidoyl] pyrrolidine-1-carboximidamide (IUPAC name), is a novel biguanide with higher potency of AMP-activated protein kinase activation than metformin. Lixumistat is a novel biguanide mitochondrial protein complex 1 inhibitor of oxidative phosphorylation with anti-tumor activity. Lixumistat regulates oxidative phosphorylation to attenuate mitochondrial metabolic reprogramming and inhibit lung fibrosis. Lixumistat also suppresses B-cell activation to alleviate systemic lupus erythematosus. It has inhibitory activity against angiogenesis and cancer [63]. Unlike metformin, which is relatively hydrophilic and requires active transport to enter cells, IM156 is more hydrophobic, which makes it potentially more bioavailable to cancer cells. In addition, at equal concentrations, IM156 was more potent at decreasing the oxygen consumption rate of tumor cells compared to phenformin and metformin. It was also more effective in reducing cellular ATP production versus phenformin without an increase in the extracellular acidification rate [64]. Results clarified the beneficial effect of HL156A in reducing oral cancer development [65]. Additionally, another study shows that inhibiting autophagy is a potential approach to increase the effectiveness of metformin and/or HL156A in treating oral squamous cell carcinoma cells [66]. Moreover, published data demonstrate that HL156A suppresses multidrug resistance, which is a significant

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clinical crisis in cancer treatment and has been linked to the cellular expression of multidrug efflux transporters. Thus, HL156A, a derivative of the antidiabetic drug metformin, could be a new candidate as a potential chemotherapeutic agent in multidrug-resistant cancer cells [67].

2.5. IM176

IM176, also called as IM176OUT05 is a novel biguanide derivative that has been reported to activate AMPK, inhibiting mTOR, androgen receptor, and prostate-specific antigen (PSA). IM176 is a high soluble biguanide and activates stem cell metabolism, promotes hair regrowth and increases stemness induction and maintenance during the pluripotent stem cell generation process. IM176 inhibits mitochondrial electron transport chain activity. It has superior anti-tumoral effects in prostate cancer [68,69]. IM176 showed antitumor effects comparable to those of metformin and phenformin, and may therefore be a novel candidate for the treatment of patients with prostate cancer, including castration-resistant prostate cancer [69]. Nevertheless, the available literature is very limited as IM176 is still thoroughly studied.

2.6. Moroxydine

Moroxydine, called also as ABOB hydrochloride is a heterocyclic biguanide, also known as 4-morpholinocarboximidoylguanidine, morpholinobiguanide or N-(diaminomethylidene)morpholine-4-carboximidamide (IUPAC name). It is the metformin derivative that is mostly studied in its hydrochloride form. According to the literature, moroxydine has an antiviral effect [70] with application potential as a pesticide for the management of plant viruses [71,72]. Moroxydine has multi-antiviral activities against DNA and RNA viruses including influenza symptoms, herpes simplex, varicellazoster, measles, mumps disease, hepatitis C virus, etc. [73]. Moroxydine hydrochloride shows high anti-grass carp reovirus activity. Recent results also indicate moderate effectiveness of moroxydine for SARS-CoV-2 inhibition [74].

2.7. Proguanil and Cycloguanil

Proguanil, also known as chlorguanide, chloroguanide or (1*E*)-1-[amino-(4-chloroanilino)methylidene]-2-propan-2-ylguanidine (IUPAC name) and cycloguanil, often called chlorguanide triazine or 1-(4-chlorophenyl)-6,6-dimethyl-1,3,5-triazine-2,4-diamine (IUPAC name), are metformin derivatives with antimalarial effects [70]. Proguanil is inactive, but its cyclic metabolite cycloguanil is active [75]. Proguanil has gained attention due to its anti-tumor effects [76], which is based on reducing tumor hypoxia, inducing mitochondrial dysfunction and oxidative stress, and causing DNA damage [77]. The anticancer activity of cycloguanil was also observed [78].

2.8. Metformin Sulfenamides and Sulfonamides

Metformin sulfenamides are derivatives of metformin with various promising effects. They differ in length and shape of the hydrocarbonthio chain. Metformin sulfenamides show more clearly marked anti-coagulant properties than metformin [79,80]. Another study has suggested that biguanides might have the potential in preventing brain disorders associated with diabetes complications in the future [81]. A very interesting derivative is metformin cysteine, which has been reported to improve lipid profile and fasting blood sugar and fasting blood insulin better than metformin [82]. Metformin sulfonamides show similar effects in anti-coagulation properties as metformin sulfenamides [79,80,83,84].

2.9. LysMET

LysMET, a novel polypeptide derivative of metformin, is synthesized through a one-step reaction involving poly-l-lysine and dicyandiamide under acidic conditions and heat. This prepared derivative has the potential to serve as both an anticancer therapeutic and a gene carrier. In experiments, LysMET showed similar effectiveness to MET in suppressing HT-29 colon cancer cells, highlighting the importance of the biguanide component. Furthermore, LysMET demonstrated

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favorable attributes for effectively controlling tumor progression, indicating its dual role as both a drug and gene carrier [85].

2.10. Artesunate-Metformin Conjugate AM2

Artesunate-metformin conjugate AM2 was synthesized by Lin et al. [86] by two steps. At the beginning, metformin hydrochloride reacted with sodium hydroxide in dichloromethane to obtain free metformin. Such prepared metformin was subjected to the reaction with artesunate, a derivative of artemisinin, in dichloromethane under the catalysis of 4-Dimethylaminopyridine and carbonyldiimide hydrochloride. The author found that the novel artesunate-metformin conjugate, AM2, shows significant potential as a highly effective anti-bladder cancer agent. It inhibits the proliferation, migration, and lipogenesis of bladder cancer cells, specifically targeting the Clusterin/SREBP1/FASN signaling pathway. AM2 was shown to be far more potent than both cisplatin and metformin alone, exhibiting minimal toxicity to normal cells. These results suggest that AM2 could become a promising therapeutic option for bladder cancer treatment.

2.11. Metformin Salts

Metformin hydrochloride is the most well-known salt of metformin. It is also called metformin extended-release, metformin ER, or metformin XR. While both forms of metformin contain the same active ingredient, they are taken differently and have some differences in side effects. Metformin is usually dosed as a 500 mg tablet taken twice daily with food. However, there is also an 850 mg tablet that can be taken once daily. Metformin hydrochloride is the extended-release version of metformin and only needs to be taken once daily with food. It also has fewer side effects and lasts longer than regular metformin. Both metformin and metformin hydrochloride are approved to manage type 2 diabetes mellitus. Studies comparing metformin and metformin hydrochloride for type 2 diabetes mellitus found that metformin hydrochloride is relatively comparable to metformin in effectiveness. In fact, metformin hydrochloride may be superior to regular metformin due to its lower side-effect profile and ease of application. Those with type 2 diabetes mellitus may be more inclined to take a once-daily metformin pill instead of a twice-daily pill. Study by Derosa et al. have found that metformin hydrochloride was more effective than metformin in treating patients with type 2 diabetes. Those taking metformin hydrochloride experienced better glycemic control and lipid metabolism compared to metformin [87]. Another study demonstrated the therapeutic equivalence of metformin hydrochloride and metformin over a 24-week period for patients with type 2 diabetes mellitus. This confirms metformin hydrochloride as an important treatment option for patients in whom dosing frequency could affect medication compliance and compromise treatment outcomes [88].

This study was confirmed by Akram, who found that metformin hydrochloride may improve the quality of therapy and the safety profile relative to a conventional dosage form in patients with type 2 diabetes mellitus [89]. Similar results were observed by Tan [90] with some limitations. The authors included only five randomized trials and one observational study, and long-term endpoints were not identified for metformin hydrochloride and metformin use. A more recent study [91] explains, that the difference between the two formulations is not statistically significant. Metformin hydrochloride was statistically associated with a reduced cumulative incidence of dyspepsia compared to metformin. Moreover, metformin hydrochloride was found to improve total cholesterol and low-density lipoprotein cholesterol compared to metformin [92]. The same observations were given in another literature [93]. However, the use of metformin hydrochloride was associated with an increase in triglycerides

There is very limited literature related to metformin hydrobromide and hydroiodide. A recent study has provided only information about the metformin hydrobromide synthesis without any further thorough study [94]. Surprisingly, the metformin hydroiodide is mentioned in literature only in the context of solar cell passivation [95].

Metformin acetate belongs to biguanides which have been already almost forgotten. It was synthesized with antibacterial effect expectations [96]. In this study, the authors synthesized also complexes with Cu (II), Ni (II), Mn (II) and Zn (II). These complexes were much more microbially

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active than metformin acetate. With respect to the above-mentioned, this led to a loss of interest in studying metformin acetate and recent literature is missing.

Metformin embonate, also known as metformin pamoate or 4-[(3-carboxy-2-hydroxynaphthalen-1-yl)methyl]-3-hydroxynaphthalene-2-carboxylic acid;3-(diaminomethylidene)-1,1-dimethylguanidine (IUPAC name), is a drug widely known for its use in anti-diabetic treatments [97]. However, its anti-diabetic effectiveness is lower compared to metformin.

A series of novel derivatives, metformin threonate, metformin tartrate, metformin citrate, metformin mesylate and metformin maleate were synthesized. Among them, metformin threonate exhibited the strongest potency on AMP-activated protein kinase activation with a better safety profile [94,98].

3. Conclusions and Future Perspectives

Metformin has garnered significant attention due to its multispectral mechanism of action, which can be enhanced through derivatization. The review provides details on the types and importance of metformin derivatives, along with their advantages over metformin. Based on the published material the authors were able to gather, several tentative conclusions can be derived.

The formulation of metformin hydrochloride has been designed to facilitate a more gradual release of the drug in the primary absorption site, namely the upper gastrointestinal tract. This improvement enhances tolerability and patient compliance by reducing the frequency of administration and the occurrence of adverse events.

Phenformin, unlike metformin, has been demonstrated to effectively suppress the inflammatory response in the skin and exhibits greater potency as a mitochondrial inhibitor compared to metformin.

The unique mechanism of action and safety profile of Imeglimin, in comparison to metformin, potentially address the current gap in the treatment of type 2 diabetes mellitus.

Lixumistat is more hydrophobic than metformin, making it potentially more bioavailable to cancer cells.

Derivative IM176 shows antitumor effects comparable to those of metformin and phenformin.

Derivatives like moroxydine exhibit antiviral effects through a broad-spectrum action against both DNA and RNA viruses, and they are capable of inhibiting the SARS-CoV-2 virus as well.

Proguanil and cycloguanil, both derivatives of metformin, demonstrate antimalarial effects. Furthermore, their potential anti-tumor effects show promise.

Metformin sulfenamides and sulfonamides demonstrate more evident anti-coagulant properties than metformin itself.

Another derivative LysMET showed similar effectiveness to MET in suppressing HT-29 tumors.

Artesunate-metformin conjugate AM2 was shown to be far more potent than metformin alone, exhibiting minimal toxicity to normal cells. These results suggest that AM2 could become a promising therapeutic option for bladder cancer treatment.

These findings offer direct evidence that new metformin derivatives could serve as a promising foundation for designing and synthesizing novel biguanide-based compounds with more advanced effects than their parent drug, metformin. In practice, a broad spectrum of possibilities exists for the next synthesis work, as metformin derivatives have the potential to contribute advancements to the studied subject, despite some of the previously mentioned studies indicating no evidence for a decreased risk of various cancer types associated with metformin use.

The subsequent derivatives should meet crucial requirements, foremost among them being the mitigation of lactic acidosis, a serious side effect for some patients. Additionally, drug administration should be as comfortable as possible, facilitated by an extended release. In various clinical diagnoses, discernible targeted effects are essential, anticipating the potential use of metformin derivatives in adjuvant therapy post-cancer treatment. Controlled weight loss, as a favorable side effect of metformin derivatives, should also be investigated for its role in obesity prevention, thereby mitigating associated risks.

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