

# View on Metformin: Antidiabetic and Pleiotropic Effects, Pharmacokinetics, Side Effects and Sex-Related Differences

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**Abstract:** Metformin is a synthetic biguanide used as an antidiabetic drug in type 2 diabetes mellitus, achieved by studying the bioactive metabolites of *Galega officinalis* L. It is also used off-label in various other diseases, such as subclinical diabetes, obesity, polycystic ovary syndrome, etc. In addition, metformin is proposed as an add-on therapy for several conditions, including autoimmune diseases, neurodegenerative diseases, and cancer. Although metformin has been used for many decades, it is still the subject of many pharmacodynamic and pharmacokinetic studies in light of its extensive use. Metformin acts at mitochondrial level by inhibiting the respiratory chain, thus increasing the AMP/ATP ratio and, subsequently, activating the AMP-activated protein kinase. However, several other mechanisms have been proposed, including binding to presenilin enhancer 2, increasing GLP-1 release, and modification of microRNA expression. Regarding its pharmacokinetics, after oral administration, metformin is absorbed, distributed, and eliminated, mainly through the renal route, using transporters for cationic solutes, since it exists as an ionic molecule at physiological pH. In this review, particular consideration has been paid to literature data from the last 10 years, deepening the study of clinical trials inherent to new uses of metformin, the differences in effectiveness and safety observed between the sexes, and the unwanted side effects. For this last objective, metformin safety was also evaluated using both EudraVigilance and Vigibase, respectively, the European and WHO databases of the reported adverse drug reactions, to assess the extent of metformin side effects in the real-life use.

**Keywords:** AMPK; miRNA; antidiabetic drugs; ADRs; sex-differences; ADMET; pharmacovigilance; T2DM

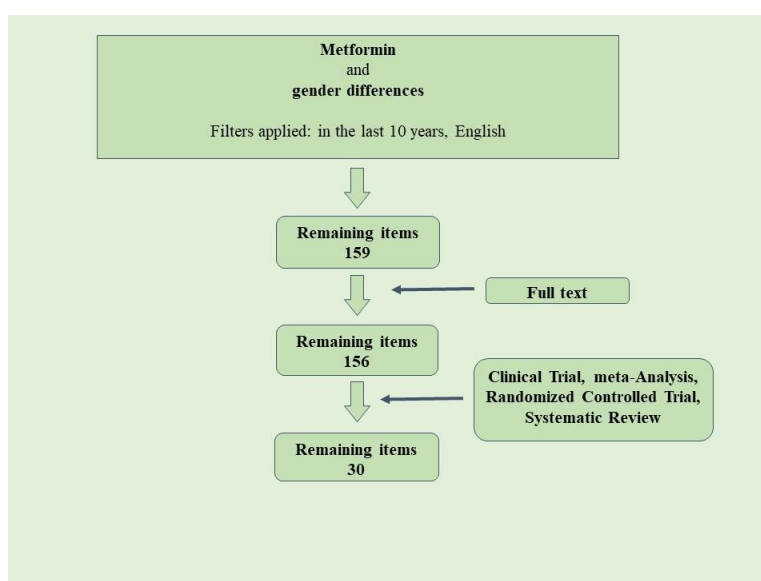


Figure S1: Flowchart of articles obtained by the PubMed search for metformin up to February 2024.

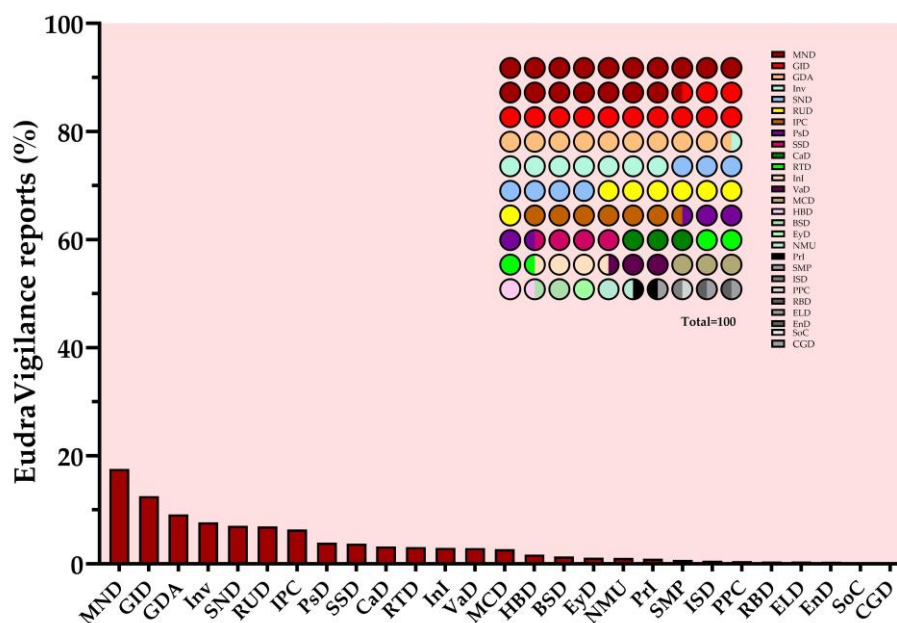


Figure S2: Reports of spontaneous ADRs on metformin obtained by consulting EudraVigilance.

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