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Review Article

Thiazolidinediones as potent anticancer agents: A Review

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Abstract

Heterocyclic compounds and their derivatives has been an interesting field in medicinal chemistry because of their biological and pharmacological properties. Heterocyclic compounds are cyclic compounds in which the ring contains carbon, one or more atoms of other elements, commonly called as hetero atoms. Heterocyclic compounds usually contain hetero atoms like nitrogen, sulphur and oxygen. This review reflects the contribution of Thiazolidinedione as a scaffold to develop novel class of anticancer agents through PPAR-γ activation mechanism.

Keywords: Anticancer activity, Cancer, PPAR-γ, Thiazolidinedione.

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1. Introduction

Cancer is a disease/ unwanted growth of cells with a large impact on the people's health in the world, makes it the second leading cause of death after cardiovascular diseases [1]. According to the World Cancer Report 2014, cancer affected 8.2 million lives in the year 2012 [2], and is believed to be the primary cause of death in the coming years.

Lung, liver, stomach and bowel cancer are the most common cancer leading to deaths worldwide, accounting for nearly a half of all cancer deaths. The five most common types of disease diagnosed in 2012 were lung, prostate, colorectal, stomach and liver cancer among men[2]. Among the various types of malignant tumors reported so far breast cancer is the second most prominent reason for deaths among the women followed by colorectal, lung, cervix and stomach cancer [3]. Colorectal cancer is the third leading cause of death in united states with 50% patients lost their lives in the year 2010 [2].

In search of potential anticancer agents, enormous efforts aimed at the implementation of new treatment strategies resulting in the development of scaffolds containing heterocyclic structure as their key structural design. Heterocyclic compound play an important role in cancer therapy. Among them Researcher's interest pointed towards thiazolidinedione, a privileged scaffold in modern medicinal chemistry, considering its wide spectrum of biological activities and affinity towards various biological targets [4].

Thiazolidinedione (TZDs), also called glitazones is a five-membered carbon ring molecules containing two heteroatoms (nitrogen and sulfur). One carbonyl group in the thiazole at position 4 and another at position 2 makes the heterocyclic compound a thiazolidine-2,4-dione[5].

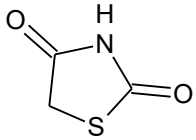

Fig.1: Thiazolidine-2, 4- dione

The biological activities exhibited by TZD includes anti-hyperglycaemic[6], antimicrobial[7], antiviral[8], antioxidant[9], anticancer[10], anti-inflammatory[11], anti-plasmodial, alpha glucosidase inhibitory, xanthine oxidase inhibitory activity etc. because of wide profile, thiazolidinediones are still in research for better, safer and potential pharmacological agents.

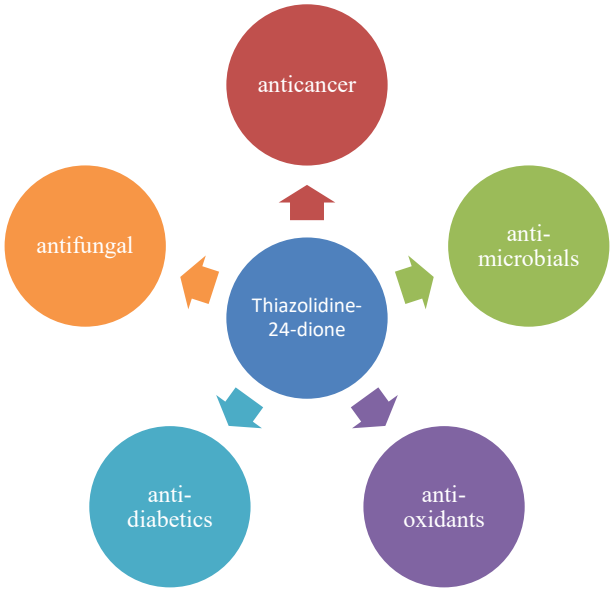

Fig. 2: Pharmacological activities of thiazolidine-2,4-dione

TZDs are one of the main heterocyclic ring systems having therapeutic importance when combined with other heterocyclic rings. For the exploration of novel and highly active therapeutic compounds the combination of two pharmacophores into a single molecule is an interesting, effective and mostly used direction in modern medicinal chemistry.

TZD ring has been used as a scaffold to develop this novel class of anticancer agents, encouraged by the literature report that toxicity of troglitazone is not due to TZD ring [12].TZD moiety is directly connected to an N-heterocyclic ring so as to lower their toxic effects [13].

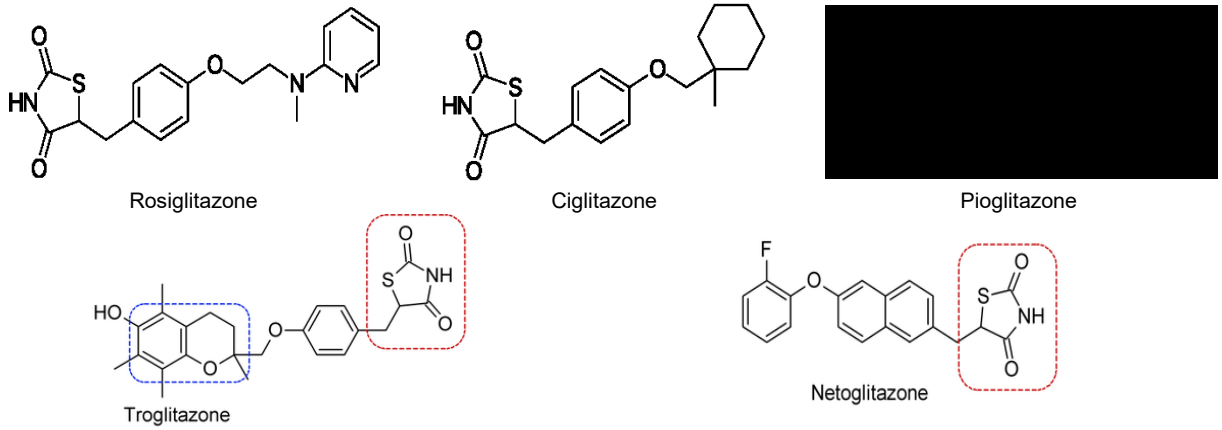

Fig.3: Drugs containing thiazolidine-2,4-dione

There are several mechanisms of anticancer activity of TZDs including

- Induction of apoptosis
- Cell differentiation
- Cell cycle arrest

Some of the TZDs are designed for the treatment of human cancers expressing high levels of Peroxisome Proliferator-activated Receptor gamma (PPAR-γ), which is expressed in many human tumours including lung, breast, colon, prostate and bladder cancer. It is assumed that activation of PPAR-γ mediates their anticancer activity [14].

PPAR-γ, Peroxisome Proliferator-activated Receptor gamma, also known as the glitazone receptor, or NR1C3 is a type II nuclear receptor that in humans is encoded by PPARG gene. PPAR-γ is the master regulator of adipogenesis and the pharmacological target of the TZD class of insulin sensitizers. As metabolic regulators PPARs control the expression of genes involved in adipocyte differentiation, lipid and glucose metabolism, and as well as inflammation in immune cells and cell proliferation .Apart from the known metabolic actions, PPAR-γ has also been shown to be over expressed in numerous human cancers including breast, bladder, prostate, colon and thyroid.

PPAR-γ agonist exhibit antitumor activities. It was also proposed to induce apoptosis in some malignant cell lineages. *In-vivo* and *in-vitro* studies have revealed antiproliferative and proapoptotic actions of PPAR-γ agonists indicating that PPAR-γ could be a promising therapeutic target for the treatment of cancers[15].

2. Antitumor activity of thiazolidinediones

Thiazolidinediones (TZDs), like troglitazone, rosiglitazone, pioglitazone, and ciglitazone are some of the high-affinity ligands for PPAR-γ and are clinically being used as oral hypoglycemic agents in type 2 diabetes mellituspatients. TZDs activate the PPAR-γ causing transcriptional activation of insulin-sensitive genes in glucose homeostasis in a way which imitates the genomic effects of insulin. In addition, TZDs have been found to decrease colorectal, lung and breast cancer risks in diabetic patients.

TZDs mediate their antitumor activities through the induction of cell cycle arrest, apoptosis, and redifferentiation. But the exact antiproliferative mechanisms of TZDs remain unclear; various evidences show that TZDs have both PPAR-γ dependent and independent mechanisms.

PPAR-γ dependent mechanisms include the induction of pro-apoptotic proteins, phosphatase and tensin homolog (PTEN), p53, and BAD; and recusing the level of the anti-apoptotic proteins Bcl-2, Bcl-xL, and survivin), followed by the down-regulation of ERK1/2, which induce apoptosis via the mitochondrial pathway.

The PPAR-γ independent action of TZDs, which targets multiple signalling pathways, is mediated through the energy restriction mimetic effect and the induction of starvation-associated cellular responses [16].

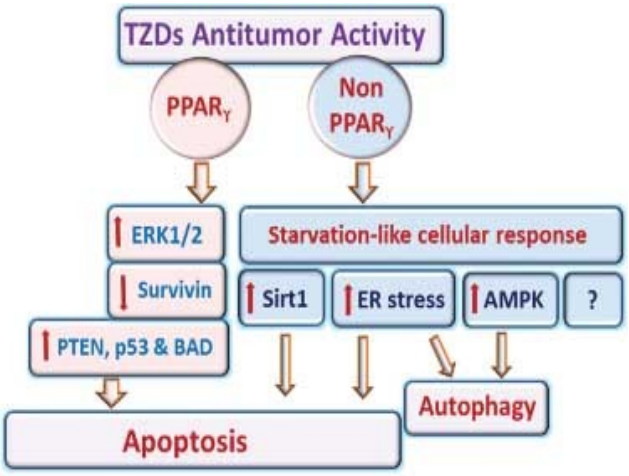

Fig. 4: PPAR γ -dependent and independent effects of thiazolidinedione

3. Conclusion

The thiazolidine-2, 4-dione derivatives showing anticancer activity are mainly derivatives modified in the position 5 of the thiazolidine-2, 4-dione derivatives. The fifth position of thiazolidine-2, 4-diones being relatively more reactive, hence most of the modification at this position exhibits a wide spectrum of pharmacological properties. TZD moiety is directly connected to an N-heterocyclic ring in order to improve its anticancer activity. Thus the dose required for anticancer activity of TZD would be significantly lower than that required to bring hypoglycaemic activity.

Conflict of Interest: No conflict of interest.

Acknowledgements: None

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