Check for updates

REVIEW

REVISED Fenofibrate in cancer: mechanisms involved in anticancer activity [version 2; peer review: 1 approved, 1 approved with reservations]

Tomas Koltai

Centro de Diagnostico y Tratamiento de la Obra Social del Personal de la Alimentación, Buenos Aires, 1618, Argentina

v2 First published: 26 Feb 2015, 4:55
<https://doi.org/10.12688/f1000research.6153.1>
 Latest published: 07 Jul 2015, 4:55
<https://doi.org/10.12688/f1000research.6153.2>

Abstract

Objective: To review the mechanisms of anti-cancer activity of fenofibrate (FF) and other Peroxisome Proliferator Activator Receptor α (PPAR α) agonists based on evidences reported in the published literature.

Methods: We extensively reviewed the literature concerning FF as an off target anti-cancer drug. Controversies regarding conflicting findings were also addressed.

Results: The main mechanism involved in anti-cancer activity is anti-angiogenesis through down-regulation of Vascular Endothelial Growth Factor (VEGF), Vascular Endothelial Growth Factor Receptor (VEGFR) and Hypoxia Inducible factor-1 α (HIF-1 α), inhibition of endothelial cell migration, up-regulation of endostatin and thrombospondin-1, but there are many other contributing mechanisms like apoptosis and cell cycle arrest, down-regulation of Nuclear Factor Kappa B (NF- κ B) and Protein kinase B (Akt) and decrease of cellular energy by impairing mitochondrial function. Growth impairment is related to down-regulation of Phospho-Inositol 3 Kinase (PI3K)/Akt axis and down-regulation of the p38 map kinase (MAPK) cascade. A possible role should be assigned to FF stimulated over-expression of Tribbles Homolog-3 (TRIB3) which inhibits Akt phosphorylation. Important anti-cancer and anti-metastatic activities are due to down-regulation of MCP-1 (monocyte chemotactic protein-1), decreased Metalloprotease-9 (MMP-9) production, weak down-regulation of adhesion molecules like E selectin, intercellular adhesion molecules (ICAM) and Vascular Endothelial Adhesion Molecules (VCAM), and decreased secretion of chemokines like Interleukin-6 (IL-6), and down-regulation of cyclin D-1. There is no direct link between FF activity in lipid metabolism and anticancer activity, except for the fact that many anticancer actions are dependent from PPAR α agonism. FF exhibits also PPAR α independent anti-cancer activities.

Conclusions: There are strong evidences indicating that FF can disrupt growth-related activities in many different cancers, due to

Open Peer Review

Approval Status

	1	2
version 2 (revision) 07 Jul 2015	 view	 view
version 1 26 Feb 2015	 view	

1. **Krzysztof Reiss**, Louisiana State University
Health Sciences Center, New Orleans, USA

2. **Jarosław Czyż**, Jagiellonian University,
Krakow, Poland

Any reports and responses or comments on the article can be found at the end of the article.

anti-angiogenesis and anti-inflammatory effects. Therefore FF may be useful as a complementary adjunct treatment of cancer, particularly included in anti-angiogenic protocols like those currently increasingly used in glioblastoma. There are sound reasons to initiate well planned phase II clinical trials for FF as a complementary adjunct treatment of cancer.

Keywords

Fenofibrate, cancer, PPAR, angiogenesis, metastasis, prostate, cancer, glioblastoma, melanoma, nelfinavir

Corresponding author: Tomas Koltai (tkoltai@hotmail.com)

Competing interests: No competing interests were disclosed.

Grant information: The author(s) declared that no grants were involved in supporting this work.

Copyright: © 2015 Koltai T. This is an open access article distributed under the terms of the [Creative Commons Attribution License](#), which permits unrestricted use, distribution, and reproduction in any medium, provided the original work is properly cited. Data associated with the article are available under the terms of the [Creative Commons Zero "No rights reserved" data waiver](#) (CC0 1.0 Public domain dedication).

How to cite this article: Koltai T. **Fenofibrate in cancer: mechanisms involved in anticancer activity [version 2; peer review: 1 approved, 1 approved with reservations]** F1000Research 2015, 4:55 <https://doi.org/10.12688/f1000research.6153.2>

First published: 26 Feb 2015, 4:55 <https://doi.org/10.12688/f1000research.6153.1>

REVISED Amendments from Version 1

Version 2 contains a detailed description of fenofibrate activity on cell membranes and mitochondria. It also highlights differences between fenofibrate and fenofibric acid regarding pharmacological activity on cancer tissues. Figures 1 and 8 have been added for a better understanding of these issues. Table 6 was modified updating references. Reference 158 was also modified and 2005 was replaced by the correct year: 2015. Also, ten new references were added.

See referee reports

Abbreviations

FF: Fenofibrate /HUVEC: Human vascular endothelial cells /MCP-1: Monocyte chemotactic protein-1 /VCAM-1: Vascular cell adhesion molecule 1 /ICAM-1: Intercellular adhesion molecule-1 /VEGF: Vascular endothelial growth factor /VEGFR: Vascular endothelial growth factor receptor /HIF: Hypoxia inducible factor /PPAR: Peroxisome proliferator activator receptor FGF: Fibroblast growth factor /bFGF: basic fibroblast growth factor /TSP-1: Thrombospondin-1 /RXR: Retinoid X receptor /ATRA: All transretinoic acid /ER: Endoplasmic reticulum /RCC: Renal cell carcinoma /PDGF: Platelet derived growth factor /TRIB-3: Tribbles homolog 3 /IGF: Insulinlike growth factor /PEG2: Prostaglandin E2 /CTMP: C-terminal modulator protein

(which inhibits AKT phosphorylation) /SCC: Squamous cell carcinoma /SREBP: Steroid regulatory element binding proteins /FAS: Fatty acid synthase.

Introduction

Fenofibrate (FF) is a drug of the fibrate class (a fibric acid derivative) (for chemical structure, see [Figure 1](#)) that has been used since 1975 to reduce cholesterol (LDL and VLDL) and triglyceride levels and increase HDL in patients at risk of cardiovascular disease and for treatment of atherosclerosis (1 and 47). FF is one of the most commonly prescribed fibrates, and has a well known efficacy and tolerability profile¹.

FF seems to lower lipid levels by activating peroxisome proliferator-activated receptor alpha (PPAR α), a nuclear receptor which acts as a ligand activated transcriptional factor and activates lipoprotein lipase and reducing apolipoprotein CIII expression. These activities increase lipolysis and eliminate triglyceride-rich particles².

PPARs are a widely distributed family of nuclear receptors. Three isoforms have been identified: PPAR α , PPAR β/δ , and PPAR γ . Ligand binding activates these receptors that play key roles in cellular energy homeostasis, modulating glucose and lipid metabolism. PPAR α as illustrated in [Figure 2](#), is the molecular target of the fibrate class of drugs, which act as agonistic ligands of PPAR α ([Figure 3](#)). Other fibrates like clofibrate and bezafibrate are also ligands for this receptor. Poly-unsaturated fatty acids are the natural ligands.

Figure 1. Fenofibrate is quickly cleaved through hydrolysis to fenofibric acid (the active form of this pharmaceutical)- FF and fenofibric acid may exert different anti-cancer pharmacological effects as will be later considered. Unprocessed FF is capable of interacting with biological membranes. Fenofibric acid is a potent PPAR α agonist that does not interact with membranes.

PPAR α activation by ligand binding

Figure 2. Ligands of PPAR α like poly-unsaturated fatty acids or fenofibrate penetrate the cell and meet the receptor in the nucleus. Upon ligand binding, PPAR α dimerizes with RXR (retinoic X receptor) and both interact with peroxisome proliferators responsive elements of the target gene. Coactivator proteins and RNA polymerase are recruited and the transcription machinery is set to work (trans-activation). When co-repressor molecules are recruited, trans-repression is unleashed and no transcription is produced.

We shall not go any deeper into lipid metabolism activities of FF because our goal is to consider the effects of this pharmaceutical in cancer prevention and treatment rather than in cardiovascular risk.

Before the year 2000, all publications on FF considered anti-lipogenic properties of this drug with no mention of possible anti-cancer activity.

We only found two publications of FF activities before than that may be related with cancer:

- 1) Marx *et al.* (1999) describe that FF reduces the expression of vascular cell adhesion molecule 1 (VCAM-1) in human endothelial cells³.
- 2) Shu *et al.* (2000) observed that PPAR α or PPAR γ reduce secretion of MMP-9 in certain cells (human monocytic THP-1 cells)⁴.

In 2002 two findings on FF anti-cancer therapy were important:

- 1) It was demonstrated that PPAR α and PPAR δ down-regulate NF-kB induced translocation to the nucleus in endothelial cells⁵ and
- 2) PPAR α activators inhibited endothelial cell migration by targeting Akt phosphorylation in endothelial cells⁶.

FF has the capacity to induce hepatocarcinoma in rodents, but this effect seems specific for this species, as in humans it has been shown to have cytotoxic effect on HepG2 hepatoma cell line at high concentrations and in a dose dependent manner⁷.

Varet *et al.* (2003)⁸ demonstrated that FF inhibits angiogenesis *in vitro* and *in vivo*.

MCP-1 (monocyte chemoattractant protein-1) is a protein that recruits and activates monocytes during inflammatory processes but also plays a role in cancer: it increases proliferation and invasion of CaP cells (prostate cancer)⁹. FF inhibits expression of MCP-1 on activated endothelial cells¹⁰.

PPAR α agonists like FF were found to inhibit endothelial VEGFR2¹¹ expression.

In diabetic II hyperlipidemic patients, FF decreased E-selectin by 10% and ICAM-1 by 4% and no change of VCAM-1 was detected¹².

Figure 3. Simplified PPAR α dependent mechanism of action of fenofibrate on lipid metabolism.

But the first real hint towards a possible anticancer activity of FF was provided by Holland *et al.* in 2004¹³ who showed by transcriptome analysis of endometrial cancer cells an overexpression of PPAR α . This finding led them to the investigation of FF activity on tumor cells. FF reduced proliferation and increased apoptosis of cancer cells. At the same time, a second publication¹⁴ showed the FF potential to reduce metastasis of melanoma cells in an experimental setting.

In oophorectomized rats, treated with estradiol and FF for 30 days, the uterine mass decreased, uterine glands had normal structure and there were no cases of atypical hyperplasia¹⁵.

Kubota *et al.*¹⁶ found that apoptosis induced by FF in cultured human hepatocytes was due to caspase-dependent apoptosis by inhibiting phosphorylation of Akt, in a PPAR α independent manner.

The role of chemokines produced by different stromal cells stimulating proliferation and angiogenesis in cancer tissues is well known. FF exerts a monocyte suppressing activity and reduces secretion of IL-6 and MCP-1¹⁷.

Studying the possible anti-rheumatic activity of FF it was observed that this compound inhibits NF-kB¹⁸.

After these preliminary hints indicating the FF possible anti-cancer activities of FF, great amount of research and publications were dedicated to this issue. We summarized these findings in [table 1](#) to [table 15](#) according to anti-cancer activity disclosed.

FF anticancer mechanisms

On artificial grounds, but for better understanding, we have presented the anti-cancer activity of FF according to the main pro-tumor factor/pathway affected by the drug.

In the field of angiogenesis there is clinical experience with FF besides the laboratory experimental setting. In the research by Blann *et al.*¹⁹, hyperlipidemic patients treated with FF showed reduced lipidemia and plasmatic VEGF. No changes in VEGFR levels were seen. (Antiangiogenic mechanisms are summarized in [Figure 4](#)).

There is a tissue where FF has a pro-angiogenic effect: human retina. An anti-apoptotic property of FF in human retinal endothelial cells was reported by Kim J *et al.* in 2007²⁴. FF potentially activated AMP-activated protein kinase (AMPK) and vascular endothelial growth factor (VEGF) mRNA expression. This finding was corroborated by the ACCORD medical study²⁵ in patients with diabetes type 2 where FF was shown to have protective activity in diabetic retinopathy and other diabetic microvascular complications, probably through a decrease of human retinal endothelial cells apoptosis²⁶.

This may mean that FF has a tissue specific activity that needs further investigations.

Probably the strongest and clearest evidence of the FF anti-angiogenic activity comes from the research of Panigraphy *et al.*²¹ of the Judah Folkman team and the research by Dana *et al.*²³ on HUVEC.

Angiogenesis inhibition as described in [Table 1](#) is probably one of the main anti-tumor activities of FF. Nickkho-Amiry *et al.*²⁷ showed that treatment of human endometrial cells with a PPAR α agonist leads to reduced secretion of VEGF in addition to reduced proliferation. This was potentiated by RxR (Retinoid X receptor) agonist like ATRA and inhibited by a PPAR α antagonist.

In a rat model Onalan *et al.* showed that FF caused regression of new endometriotic implants due to decreased angiogenesis²⁸.

FF was included in many multi-agent anti-angiogenic regimens. One consisted of FF, celecoxib, thalidomide with metronomic low

Figure 4. FF anti-angiogenic mechanisms.

Table 1. Angiogenesis inhibition.

Reference	FF activities
Blann AD, 2001 ¹⁹	The levels of plasma vascular endothelial growth factor and its receptor Flt-1 in patients with hyperlipidemia and atherosclerosis are lowered by fluvastatin or FF by down-regulation of VEGF and VEGFR.
Goetze S, 2002 ⁶	Both PPAR α - and PPAR γ -activators inhibited VEGF-induced migration of HUVEC. VEGF-induced Akt phosphorylation was significantly inhibited by both PPAR α - and γ -activators.
Varet J, 2003 ⁸	FF inhibits angiogenesis <i>in vitro</i> and <i>in vivo</i> , decreases bFGF induced Akt activation and COX2 expression and inhibits endothelial cell migration (the latter is attributed to disorganization of the actin skeleton).
Pozzi A, 2010 ²⁰	PPAR α agonists down-regulate angiogenesis by down-regulating epoxyeicosatrienoic acids synthesis.
Panigraphy D, 2008 ²¹	FF produces many anti-angiogenesis effects and suppresses tumor growth through direct and indirect angiogenesis inhibition: inhibits endothelial cell proliferation, decreases VEGF, increases TSP-1 and endostatin.
Zhou J, 2012 ²²	Activation of PPAR α suppresses hypoxia-inducible factor-1 α (HIF-1 α) signaling in cancer cells. PPAR α activation promotes HIF-1 α degradation in these cells. This was further confirmed using proteasome inhibitors, which reversed PPAR α -mediated suppression of HIF-1 α expression under hypoxia.
Dana N, 2013 ²³	In HUVEC a Matrigel assay showed that FF effectively inhibited angiogenesis.
Meissner M, 2004 ¹¹	FF and other PPAR α agonists inhibit VEGFR2 expression in HUVEC.

Table 2. FF and PPAR α agonists pro-apoptosis activities.

Reference	FF activity
Avis I, 2001 ³⁶	Exposure of breast cancer cells to a 5-LO inhibitor up-regulated PPAR α and PPAR γ expression. Cells were growth inhibited when exposed to relevant PPAR agonists.
Chinetti G, 1998 ³⁷	Macrophages activated by TNF α may suffer apoptosis by PPAR α and PPAR γ ligands.
Holland CM, 2004 ¹³	Treatment with FF significantly reduced proliferation and increased cell death in endometrial cancer cells, suggesting that altered expression of nuclear hormone receptors involved with fatty acid metabolism leads to deregulated cellular proliferation and apoptosis. PPAR α was increased more than 4-folds in endometrial cancer cells.
Kubota T, 2005 ¹⁶	FF causes caspase-dependent apoptosis in human hepatocytes by inhibiting phosphorylation of Akt, in which PPAR α is not involved. (Human hepatocytes)
Zak Z, 2010 ³⁸	FF induces effective apoptosis in mantle cell lymphoma by inhibiting the TNF α /NF- κ B signaling axis.
Wang J, 2011 ³⁹	Combination of FF and cisplatin can enhance the role of cisplatin killing lung cancer A549 cells, which may be a result of up-regulating caspase-3 and down-regulating survivin.
Li T, 2014 ⁴⁰	FF has anti-proliferation effects on breast cancer cell lines. Apoptosis was independent on the PPAR- α status with up-regulation of Bad, down-regulation of Bcl-xl, survivin and activation of caspase-3. FF produced cell cycle arrest at G0/G1 phase with down-regulation of cyclin D1, Cdk4 and up-regulation of p21, p27/Kip1. <i>In vivo</i> , FF slowed down tumor growth and induced apoptosis in the MDA-MB-231 xenograft mouse model.
Binello E, 2014 ⁴¹	FF showed anti-proliferative and pro-apoptotic effects on high-grade gliomas and anti-invasive effects on glioma stem cells.
Majeed Y, 2014 ⁴²	In angiosarcoma forming endothelial cells FF induced apoptosis, reducing Bcl-2, survivin, Akt expression and Erk proteins. No effects on normal endothelial cells.

dose cyclophosphamide and etoposide. Patients were less than 21 year old with recurrent or progressive tumors. Half of the patients obtained benefits (CR + PR + SD)²⁹.

Other metronomic anti-angiogenic multidrug protocols included FF as one of the pharmaceuticals, particularly for children with embryonal brain tumors and other malignancies^{30–32}.

The COMBAT Protocol³³ included low-dose daily temozolomide, etoposide, celecoxib, vitamin D, FF and retinoic acid and was used in 74 children with advanced refractory/relapsed solid tumors with two years overall survival of 43%.

The use of FF as part of anti-angiogenic multidrug protocols especially in pediatric cancer is constantly increasing.

Table 3. Anti-proliferation activity of FF.

Reference	FF activities
Thuillier P, 2000 ⁵⁶	Ligands for PPAR α reduce skin cancer by 30% against skin tumor promotion.
Jiao H, 2002 ⁷	FF inhibits the growth of human HepG2 cells in a dose-related manner and oxidative stress was involved in this effect.
Holland CM, 2004 ¹³	Treatment with FF significantly reduced proliferation and increased cell death in endometrial cancer cells.
Gizard F, 2005 ⁵⁷	FF inhibits vascular smooth vessel proliferation by inducing anti-oncogen p16.
Saidi SA, 2006 ⁵⁸	The combination of FF and retinoic acid is a potent inhibitor of Ishikawa endometrial cancer cell growth <i>in vitro</i> . Cell cycle arrest is produced at G1/S. Cyclin D1 was down-regulated. These results could not be reproduced <i>in vivo</i> .
Panigraphy D, 2007 ²¹	FF suppresses tumor growth through angiogenesis inhibition.
Yokoyama Y, 2007 ⁵⁹	Clofibric acid (a PPAR α agonist) significantly suppressed the growth of OVCAR-3 tumors xenotransplanted s.c. and significantly prolongs the survival of mice with malignant ascites derived from DISS cells as compared with control. Microvessel density was diminished and apoptosis was also found. VEGF and PGE2 were also diminished.
Yamasaki D, 2011 ⁶⁰	FF suppresses growth of the human hepatocellular carcinoma cell (Huh7) via PPAR α -independent mechanisms and produces G1 arrest caused by the reduction of cyclin A and E2F1 and accumulation of the cyclin-dependent kinase inhibitor p27. This activity was not modified by PPAR α antagonists. Inhibition of Akt phosphorylation by increased CTMP was also observed.
Chang NW, 2011 ⁶¹	FF highly suppresses the formation of squamous cell carcinoma in an oral-specific 4-nitroquinoline 1-oxide/ arecoline mouse model, decreases the tumor size, and increases the immunoreactivity of EGFR and COX2 in oral dysplasia, but decreases EGFR and COX2 expressions in SCC. These molecular events might be linked to the EGFR and COX2 regulatory pathways.
Huang J, 2013 ⁶²	FF is capable to suppress B-cell lymphoma growth. This growth suppression is independent of angiogenesis inhibition.
Binello E, 2014 ⁴¹	FF shows anti-proliferative pro-apoptotic effects on high-grade gliomas and anti-invasive effects on glioma stem cells.
Li T, 2014 ⁴⁰	FF has anti-proliferation effects on breast cancer cell lines.
Wang H, 2014 ⁶³	FF can inhibit the growth and migration of human ovarian cancer cell SKOV3 <i>in vitro</i> , and to some extent induce apoptosis.
Liang H, 2014 ⁶⁴	Synergistic inhibitory effects on cancer cell proliferation by simultaneous application of FF and budesonide. FF inhibited cell proliferation in both TP53 wild type and deficient lung cancer cells. The anti-proliferation effect of budesonide in TP53 wild type A549 cells was abolished in SK-MES-1 cells that do not have wild type TP53 protein.

Antiproliferative activities are summarized in [Figure 5](#).

Figure 5. Mechanisms of FF anti-proliferative activity and pro-proliferative activity in mice hepatocarcinoma.

Using a PPAR α agonist like Wy-14643 in mice injected with tumor cells showed that treated animals had a marked reduction in tumor size and vascularization³⁴.

In summary: FF increases thrombospondin synthesis, endostatin generation, decreases VEGF, COX2 and VEGFR2 expressions and prevents endothelial cells migration^{21,35}.

Apoptosis induced by FF is caspase-dependent. In the case of clofibrate, apoptosis occurs through caspase 2 and 3 activation and ER stress in Jurkat cells⁴³. Similar results were observed in Yoshida AH130 hepatoma cells⁴⁴.

PPAR α is increased in high grade renal cell carcinoma (RCC), but this does not provide any information about the functional status of this receptor, because in RCC the inhibition of PPAR α induces apoptosis and agonists produce little or no effect⁴⁵.

In 1983 Pascal *et al.*⁴⁶ investigated the cardiovascular and anti-arteriosclerotic activities of FF and demonstrated that FF inhibited platelet derived growth factor (PDGF) stimulating activity on growth of cultured smooth muscle. Ten years later Munro *et al.*⁴⁷ showed that FF is not a specific inhibitor of PDGF because smooth muscle cells growth was equally growth-inhibited by FF when the culture was stimulated with fetal calf serum, PDGF or basic fibroblast growth factor (bFGF). Our conclusion based on these two publications is that FF is a growth inhibitor in general (as least regarding vascular smooth muscle).

Anti-proliferation activity of FF has been found in many non-tumor tissues besides vascular smooth muscle, e.g. mesangial cells⁴⁸ through inhibition of PI3K/AKT and ERK1/2 signaling pathways or by overexpression of TRIB3 (tribbles homolog 3) which inhibits Akt phosphorylation and slows cell cycle or causes arrest in G1/S⁴⁹. In lymphocytes, FF also up-regulates TRIB3 causing cell cycle arrest^{50,51}.

Endothelin-1 is a protein that increases cardiac fibroblast proliferation. PPAR α agonists inhibit cardiac fibroblast proliferation down-regulating endothelin-1⁵². FF also reduced c-jun expression in cardiac fibroblasts⁵³. Endothelin-1 is an activator of the p38 mitogen activated kinase cascade. FF down-regulation of endothelin-1 also down-regulates the MAPK cascade in cardiomyocytes⁵⁴.

FF reduced the IFN γ and IL-1 β -induced cell proliferation of astrocytes in culture⁵⁵.

The work by Saidi *et al.*⁵⁸ needs further discussion. The authors noticed that in Ishikawa endometrial cancer cells FF enhanced growth inhibition when ATRA was simultaneously used. ATRA by itself had no effect on growth. This is a logical finding because PPAR α forms a heterodimer with RXR before binding DNA at the peroxisome proliferators responsive element. So this synergy between FF and ATRA regarding growth inhibition seemed a PPAR α -dependent activity. Apoptosis also was increased with the combination of these drugs.

Paradoxically, RNAi inhibition of PPAR α showed only a minor reduction in FF effect and ATRA combined with FF showed minor differences in growth inhibition with or without PPAR α RNAi. After 48 hours of treatment the difference was approximately 40% less viability in cells treated with FF plus ATRA and no RNAi against those with RNAi. We hypothesize that RNAi inhibition of PPAR α needs at least 48 hours to make the viability difference. So that growth inhibition seems, at least partially, as PPAR α dependent.

They also found down-regulation of two genes: cyclin D1 (CCND1) and methionine adenosyltransferase 2 A (MAT2A), both are pro-growth genes⁵⁸. High doses of FF up-regulated p21 (cyclin-dependent kinase inhibitor 1a) and TP53.

Unfortunately FF and FF plus ATRA showed no differences in tumor size and growing *in vivo* compared with control group receiving no drugs.

The work by Chang *et al.*⁶¹ suggests that FF may be useful for prevention of oral SCC because in an experimental setting FF was capable of reducing the incidence of tumors and also the progression from pre-neoplastic stage to SCC. FF at low doses lacked anti-tumor activity.

In spite of the known fact that glucocorticoids induce chemotherapy resistance in most of the solid tumors⁶⁵, Liang *et al.*⁶⁴ found that FF and budesonide had synergistic anti-proliferative effect on lung cancer cells with intact TP53.

Inflammation plays a very important role in carcinogenesis and tumor progression. NF-kB pathway is an essential actor of the pro-inflammatory and anti-apoptotic activity⁶⁶⁻⁶⁸.

NF-kB pathway increases angiogenesis, proliferation, anti-apoptosis, metastasis and inhibition of differentiation⁶⁹.

FF has the capacity to down-regulate NF-kB activity according to evidences gathered in Table 4. Through this PPAR α -dependent mechanism, FF exerts anti-inflammatory activity. Besides, it also has non PPAR α -dependent anti-inflammatory activity through up-regulation of SHP (small heterodimer partner).

Evidences reported in Table 4 strongly support the FF anti-inflammatory activity mediated through NF-kB down-regulation and also PPAR α independent mechanisms.

One of the proposed mechanisms of FF inhibiting NF-kB activity is depicted in Figure 6.

The research studies reported in Table 5 are evidence of down-regulation of Akt phosphorylation by FF, but Piwowarczyk *et al.*⁸² working with prostate cancer cells (DU-145) and endothelial cells (HUVEC) co-cultures found that FF increased levels of phosphorylated Akt in both HUVEC and DU-145 cells. They found that Akt phosphorylation was essential for FF increase of endothelial barrier (Figure 7).

Table 4. NF- κ B down-regulation and ant-inflammatory activity.

Reference	FF activity
Staels B, 1998 ⁷⁰	In aortic smooth-muscle cells PPAR α ligands inhibit IL-1-induced production of IL-6 and expression of COX -2 as a result of PPAR α down-regulation of NF- κ B signaling.
Xu X, 2001 ⁷¹	FF and dexamethasone reduced NF- κ B binding to its recognition site on the IL-6 promoter. FF reduced NF- κ B binding to the vascular cell adhesion molecule-1 promoter.
Ogata T, 2004 ⁷²	FF down-regulates NF- κ B in myocardium of DOCA salt rats. IL-6, COX-2, VCAM-1 and MCP-1 were also down-regulated.
Okamoto H, 2005 ¹⁸	FF inhibits NF- κ B signaling in rheumatoid synovial fibroblasts.
Yang TL, 2005 ⁷³	FF reduce NF- κ B in endothelial cells. This is a PPAR α dependent activity.
Xu J, 2006 ⁷⁴	FF reduces the signs of inflammation in murine astrocytes and down-regulated pro-inflammatory cytokines TNF- α , IL-1 β , and IL-6 by LPS-stimulated astrocytes. FF inhibited NF- κ B DNA binding activity.
Li L, 2010 ⁷⁵	FF attenuates tubulointerstitial fibrosis and inflammation through suppression of NF- κ B and transforming growth factor- β 1/Smad3 in diabetic nephropathy.
Zak Z, 2010 ³⁸	FF induces effective apoptosis in mantle cell lymphoma by inhibiting the TNF α /NF- κ B signaling axis.
Yang CS, 2013 ⁷⁶	FF improved systemic inflammatory responses through the nuclear orphan receptor SHP (small heterodimer partner) and UCP2 (uncoupling protein 2). This is PPAR α independent anti-inflammatory mechanism.
Schen W, 2014 ⁷⁷	FF down-regulated NF- κ B in endotoxin induced uveitis. All inflammatory factors like cytokine production, vessel density, vascular leukostasis and inflammatory cell infiltration was also down-regulated.
Binello E, Germano IM, 2014 ⁷⁸	FF treatment decreased glioblastoma stem cell invasion <i>in vitro</i> . Treatment decreased the expression of NF- κ B and cyclin D1 in a dose dependent and p53 independent manner.

Figure 6. Possible mechanism of NF- κ B inhibition by FF.

Mitochondrial uncoupling proteins (UCP) are mitochondrial anion carrier proteins that separate oxidative phosphorylation from ATP synthesis with energy lost as heat and reduction of mitochondrial membrane potential⁸⁹. The main function of UCP2 is the control

of mitochondria-derived reactive oxygen species. PPAR α modulates UCP2 expression⁹⁰. Pecker *et al.* have demonstrated that UCP2 exerts control on proliferation: cells (embryonic fibroblast) where UCP2 expression was down-regulated grew faster than cells

Table 5. Akt phosphorylation and down-regulation.

Reference	FF activities
Goetze S, 2002 ⁶	PPAR α agonists decrease endothelial cell migration by down-regulating Akt.
Kubota T, 2005 ¹⁶	FF causes apoptosis in cultured human hepatocytes by inhibiting Akt.
Grabacka M, 2006 ⁷⁹	PPAR α activation decreases metastatic potential of melanoma cells <i>in vitro</i> via down-regulation of Akt.
Li R, 2007 ⁸⁰	In cardiomyocytes FF and overexpression of PPAR α inhibited endothelin-1 (ET-1)-induced phosphorylation of Akt and glycogen synthase kinase3 β (GSK3 β).
Yamasaki D, 2011 ⁶⁰	FF suppresses growth of the human hepatocellular carcinoma cell via PPAR α -independent mechanisms. It produces G1 arrest caused by the reduction of cyclin A and E2F1 and accumulation of the cyclin-dependent kinase inhibitor p27. FF also leads to suppression of Akt phosphorylation by increasing C-terminal modulator protein (CTMP), which inhibits Akt phosphorylation. FF inhibits proliferation by blocking Akt activation, and CTMP is one of the key players for this effect.
Majeed Y, 2014 ⁴²	In angiosarcoma forming endothelial cells FF induced apoptosis, reducing Bcl-2, survivin, Akt expression and Erk proteins. No effects on normal endothelial cells were observed.
Kuno T, 2014 ⁸¹	FF can prevent the development of 4-NQO-induced proliferative lesions in the lung by modulating the insulin-IGF axis. FF significantly reduced the serum insulin and insulin-like growth factor (IGF)-1 levels, and decreased the immunohistochemical expression of IGF-1 receptor (IGF-1R), phosphorylated Akt, and phosphorylated Erk1/2 in lung adenocarcinomas.

Figure 7. Endothelial barrier enhancement due to FF.

expressing UCP2⁹¹. They also found that loss of UCP2 produced a metabolic change toward glucose metabolism, decreased fatty acid oxidation and increased proliferation.

Gamerding *et al.*¹⁶⁶ found that FF and cyclooxygenase inhibitors like celecoxib (COX2 inhibitor) had a similar effect to cholesterol on cellular membranes, increasing its rigidity and thickness. This conformational change of membranes produces changes in the functions of proteins embedded or spanning cell membranes, particularly in SERCA (sarcoplasmic reticulum Ca⁺⁺ ATPase9) . (Li *et al.* 2004)¹⁶⁷.

Youssef and Badr in 1998¹⁶⁸ and Zungu *et al.*¹⁶⁹ described the derangement of mitochondrial function due to peroxisome proliferator drugs. FF acts as an inducer of mitochondrial citrate synthase and NADH oxidase activity¹⁷⁰ and Scatena *et al.*¹⁷¹ identified these mitochondrial changes in the respiratory chain consisting in inhibition of NADH cytochrome c reductase activity in a dose dependent manner. They also described that mitochondrial activities of FF were PPAR α independent^{172,173}.

Wilk *et al.*¹⁵⁷ found that FF accumulated in mitochondria instead of the active form of the drug, the fenofibric acid, so that unchanged

FF was the responsible of the activity on this organelle. This finding shows that FF and fenofibric acid may exhibit different pharmacologic activities (Figure 8), and explains the efforts done to find a suitable carrier to FF that would permit the arrival of this pharmaceutical to the tumor before being cleaved to FA¹⁷⁴.

An important finding was that FF accumulates in the cell membrane fraction. FA does not¹⁷⁴. This accumulation may be the explanation why FF increases A β 42 (amyloid β peptide 42) production in mice brain¹⁷⁵.

Evidence supports that FF decreases intracellular energy through inhibition of mitochondrial enzymes in a similar way to metformin. On a theoretical basis, we may assume that there might be synergism with metformin on this ground.

PPAR α involvement with cancer metabolism has been extensively reviewed by Grabacka and Reiss⁹².

Another enzyme down-regulated by FF is FAS (fatty acid synthase)⁹³ which is highly expressed in many cancer tissues. Fatty acid synthase (FAS) is a multicomplex enzyme that intervenes in endogenous synthesis of fatty acids and particularly palmitate. Abnormal fatty acid (FA) synthesis is one of the common features of many cancer cells and FAS has been identified as part of cancer controlling networks. Human cancers that over-express FAS, are usually associated with poor prognosis^{94–98}.

The expression of adhesion molecules on the endothelial cell surface is critical for cells rolling in the vascular lumen to achieve tethering and adhesion to the vascular wall and eventually achieving

diapedesis and colonization in the case of potentially metastatic cells or leukocyte recruitment to atherosclerotic lesions.

PPAR α regulates gene expression of certain adhesion molecules in response to unsaturated fatty acids and fibric acid derivatives like FF. This control is achieved probably through inhibition of TNF α induced NF- κ B activation⁹⁹.

The research by Marchesi *et al.*⁹⁹ that demonstrated reduction in adhesion molecules with FF treatment is important for two reasons:

- 1) It was performed in humans (10 hypertriglyceridemic patients).
- 2) The amount of reduction in fasting conditions (near 45% reduction for ICAM and around 33% reduction for VCAM levels).

Empen *et al.* (2003) described 10% reduction of E-selectin after six weeks treatment with FF, but found no major changes with VCAM-1 and ICAM-1 levels¹².

Piowarczyc *et al.*⁸² demonstrated a new FF effect: increased endothelial cell adhesion to the substratum and increased adhesion between endothelial cells by activation of focal adhesion kinase (FAK). These impedes cell diapedesis through the vessel wall, which is an important objective to decrease metastatic risk. Figure 7 depicts this activity.

The production of the metastatic cascade is a complex process in which there are many successive steps that we shall not analyze in depth in this review.

Figure 8. FF is hydrolyzed in blood to fenofibric acid, which exerts PPAR α dependent metabolic switch. When FF is applied to the glioblastoma cell it accumulates in mitochondria and inhibits respiratory complex, depleting cellular ATP which activates AMPK, stimulating autophagy. The metabolic switch produced by PPAR α activity of FF plus autophagy sensitizes cells towards death.

But for a better understanding let's remember the main steps¹⁰⁶:

- 1) Primary tumor growth and angiogenesis.
- 2) Future metastatic cells free themselves from the primary tumor.
- 3) These cells degrade surrounding matrix.
- 4) Reach endothelium of vessels.
- 5) Enter blood vessels.
- 6) Circulate and survive in circulation.
- 7) Reach the target organ.
- 8) Attach to endothelial cells.
- 9) Migrate through vessel wall.
- 10) Start growth in the colonized site including angiogenesis.
- 11) Produce new metastatic cells.
- 12) Reinitiate the whole process.

Cell motility, invasion, angiogenesis and the function of connexins and adhesion molecules are an essential part of this cascade and have already been considered. In [table 8](#) we describe only specific research work relative to metastasis and FF.

COX-2 is the rate-limiting enzyme in prostaglandin synthesis that catalyzes the production of prostaglandins and thromboxanes from arachidonic acid, and has been associated with growth regulation and carcinogenesis in many tumors. The COX2/PGE2 pathway may be considered a pro-tumor pathway at least in certain cancers where elevated levels of COX2 have been identified. Most colorectal carcinomas and many adenomas exhibit this elevation^{108,109}. One of the postulated mechanisms by which COX2/PGE2 signaling stimulates cell growth is through the activation of β -catenin¹¹⁰. COX2 is implicated in breast cancer progression and invasiveness^{111,113}. In stage III breast cancer, COX2 over-expression is an unfavorable prognostic sign, and according to Kim *et al.* gives ground for using COX2 inhibitor combinations¹¹². Simeone *et al.* identified the pathway leading to increased invasiveness in breast cancer: COX2 /protein kinase C/interleukin-8/urokinase-type plasminogen activator pathway¹¹⁴. COX2 is also associated with angiogenesis and metastasis¹¹⁵.

Many cancers harbor increased COX2 activity including lung, colorectal, breast and squamous cell carcinoma of the upper digestive system^{116–118}. COX2 down-regulation is an important issue in many cancers. We have been describing the action of FF on different pro-tumor proteins in an artificially separate manner, but many of these proteins share their activity in the pro-tumor evolution or are part of the same pathway. This is the case of NF- κ B and COX2 in the progression towards cancer of Barrett's esophagus in which increased NF- κ B activity is linked to increased IL-8 and COX2 expression¹¹⁹. As described above, FF is active against both: NF- κ B and COX2.

The anticancer activities of FF are pleiotropic. Besides proliferation and angiogenesis down-regulation representing the main anti-tumoral

effects, there are many others that will be described in the next three tables like ovarian aromatase inhibition, AMPK activation, IGF-I down-regulation, etc.

The IGF-1 receptor signaling system is a contributing factor in invasion, migration and proliferation of glioblastoma and became a legitimate target in the treatment of this pathology¹²⁷. FF has experimentally shown to inhibit this system and decrease growth and invasion^{81,125,126}. A sort of IGF-1 trap was designed by D'Ambrosio *et al.*¹²⁸ that inhibited tumor growth *in vivo* and induced apoptosis.

These publications reported contrasting results: two of the showed that FF increased radiation sensitivity^{132,133} and one showed decreased radiation sensitivity¹³¹. As we shall see later, PPAR α agonists are tissue-specific and species-specific. This may explain the difference. In the first case the experiments were performed on HeLa cells and in the second and third studies, experiments were performed on squamous cell carcinoma cells. In all three cases human cells were used, so the difference may lay in tissue-specific behavior or may be due to the fact that in the second experiment the environment was particularly hypoxic.

Semaphorins are a large family of axon guidance molecules. They interact with their receptors, plexins and neuropilins, and play important roles in a growing list of diverse biological systems, including cancer progression and tumor angiogenesis. Some semaphorins can activate tumor progression and angiogenesis, while others may have the opposite effect.

There is abundant literature on semaphorins 3,4 and 7. Little is known about semaphorin-6B. It is known that there is an association between gastric cancer¹³⁶, glioblastoma¹³⁴ and certain breast cancers (MCF-7 breast adenocarcinoma cell line¹³⁵) and semaphorin-6B but the exact nature of this association is still poorly understood.

PPAR α agonists clofibrate and fenofibrate can down-regulate semaphorin-6B gene expression.

According to Ge¹³⁶, inhibition of semaphorin-6B expression via RNA interference inhibited the migration, adhesion and invasion abilities of SGC-7901 gastric cancer cells *in vitro*.

SEMA6B transcript was down-regulated in two human glioblastoma cell lines (T98G and A172) when a prolonged treatment with ATRA was performed¹³⁷.

The SEMA6B gene has a PPAR α binding site in the promoter region so that the interrelation of PPAR α and the gene effectively is present, and this interrelation is a negative one and probably exerts anti-tumoral effects.

In a large population study in Finland to assess the overall risk of prostate cancer in people taking cholesterol lowering medication, no decrease in risk was seen either with statins nor fibrates¹⁴¹. The statistics is significantly biased regarding fibrates: the population is too small (around 220 patients with prostate cancer receiving fibrates out of a total number of prostate cancer cases of 24.723).

Table 6. Decrease of cell energy and metabolic control.

Reference	FF activity
Keller BJ, 1992 ⁸³	Clofibrilic acid and ciprofibrilic inhibited stage 3 oxygen uptake in isolated mitochondria.
Zhou Z, 1999 ⁸⁴	Fenofibrilic, clofibrilic, and ciprofibrilic caused a direct dose-dependent depolarization of mitochondrial membrane potential which produced inhibition of oxydative phosphorylation and inhibition of ATP synthesis. Authors postulate that these are early events independent of PPAR α activation.
Casas F, 2000 ⁸⁵	FF or fasting suggests that the two treatments affect mitochondrial activity essentially by stimulating mitochondrial genome transcription, and increasing Cytochrome c oxidase activity.
Brunmair B, 2004 ⁸⁶	Fenofibrilic Impairs Rat Mitochondrial Function by Inhibition of Respiratory Complex I.
Nadanaciva S, 2007 ⁸⁷	FF inhibits mitochondrial Complexes I, II+III, and V.
Wilk AM, 2012 ⁸⁸ and 2015 ¹⁵⁷	In glioblastoma FF is accumulated in the mitochondrial fraction, followed by an immediate impairment of mitochondrial respiration at the level of complex I of the electron transport chain. This mitochondrial action sensitizes tested glioblastoma cells to the PPAR α -dependent metabolic switch from glycolysis to fatty acid β -oxidation.
Yang CS, 2013 ⁷⁶	FF inhibits systemic inflammatory response through small heterodimer party (SHP) that acts through mitochondrial uncoupling protein 2 (UCP-2)*.

Table 7. Anti-adhesion and anti-chemokine activities.

Reference	FF activities
Marx N, 1999 ³	FF inhibits VCAM-1 transcription probably by inhibiting TNF α induced NF- κ B activation.
Rival Y, 2002 ⁵	Fenofibrilic acid and FF reduced expression of VCAM-1 in endothelial cells and diminished migration of p65 fraction of NF- κ B to the nucleus.
Marchesi S, 2003 ⁹⁹	Reduce VCAM and ICAM in hypertriglyceridemic patients.
Gervois P, 2004 ¹⁰⁰	Suppression of IL-6-induced acute phase response gene expression after <i>in vivo</i> treatment with FF. Suppression of IL-6 reduces activation of STAT3 and c-Jun.
Lefebvre P, 2006 ¹⁰¹	PPAR α inhibits genes induced by NF- κ B, such as VCAM-1, COX-2, and IL-6.
Ryan KE, 2007 ¹⁰²	FF decreased TNF α , IL-6 IL-1 beta VCAM and ICAM in obese glucose tolerant men after 6 weeks of treatment.
Rosenson RS, 2007 ¹⁰³	FF lowered fasting and postprandial VCAM-1 (-11%) and fasting and postprandial ICAM-1 (-15%) in patients with metabolic syndrome and hypertriglyceridemia.
Lee JW, 2007 ¹⁰⁴	FF repressed IFN- γ and IL-17 expression in isolated T cells. FF also repressed the expression of the genes encoding 3 chemokines, CXCL10, CCL2, and CCL20, and repressed CXCL10 gene promoter activity in tumor necrosis factor- α -treated HT-29 cells.
Li H, 2007 ¹⁰⁵	The E-selectin and ICAM-1 secreting could be inhibited by FF in endothelial cells.
Piwowarczyc K, 2014 ⁸²	FF decreased cancer cell diapedesis by augmenting endothelial cell adhesion to the substratum. This was accompanied by the activation of ROS signaling, Akt and focal adhesion kinase (FAK) phosphorylation, in the absence of cytotoxic effects in endothelial cells.

Table 8. Anti-metastatic activity.

Reference	FF activities
Grabacka M, 2004 ¹⁴	Inhibition of melanoma metastases by FF.
Grabacka M, 2006 ⁷⁹	PPAR α activation decreases migration, colony formation and metastatic potential of Human and mice melanoma cells <i>in vitro</i> via down-regulation of Akt and ERK $\frac{1}{2}$.
Wybieralska E, 2011 ¹⁰⁷	Two parameters crucial for cancer cell metastatic potential, i.e. cell motility and gap junctional coupling, are inhibited by FF in DU 145 prostate cancer cells decreasing invasive potential.

Table 9. FF as COX2 down-regulator.

Reference	FF activities
Chen XR, 2007 ¹²⁰	In a brain damage experimental model performed in rats, Chen <i>et al.</i> demonstrated that FF improved neurological recovery by anti-inflammatory effects: decrease in iNOS, COX2 and MMP9 expression.
Varet J, 2003 ³	Reduced COX2 expression.
Ogata T, 2004 ⁵²	In DOCA salt hypertensive rat model, FF reduced COX 2 expression, besides decreasing IL-6, VCAM-1 and MCP-1.
Chen YJ, 2008 ¹²¹	FF reduced COX2 expression in kidney of diabetic rats.
Lee DL, 2011 ¹²²	Similar results as in Ogata T: in a DOCA salt hypertensive rat model FF reduced COX2 and IL-6 expression.
Chang NW, 2011 ⁶¹	FF reduces COX2 expression in an oral SCC experimental model.
Panigraphy D, 2008 ²¹	Cox 2 was reduced in melanoma B16-F10 cell line when treated with FF.
Alvarez de Sotomayor M, 2007 ¹²³	FF decreased COX1 and COX2 in endothelium of resistance arteries in rats.
Ramanan S, 2008 ¹²⁴	Irradiating a murine microglial cell line with γ -rays led to increased expression of IL-1 β and TNF α , Cox2. FF significantly decreased over-expression probably through NF-kB down-regulation.

Table 10. Other anti-cancer activities: IGF-1 signaling down-regulation.

Reference	FF activities
Urbanska K, 2008 ¹²⁵	In medulloblastoma cell lines, FF inhibits IGF-1 and growth by cell cycle arrest and induces apoptosis.
Drukala J, 2010 ¹²⁶	ROS accumulation and IGF-IR inhibition contribute to FF/PPAR α mediated inhibition of glioma cell motility <i>in vitro</i> .
Kuno T, 2014 ⁶¹	FF exerts modulation of insulin-IGF-IGFR axis.

Table 11. Other anti-cancer activities: anti-hormonal activity.

Reference	FF activities
Toda K, 2003 ¹²⁹	FF inhibits ovarian estrogen synthesis by suppressing the aromatase mRNA expression. Functional PPAR α is indispensable for the inhibitory action of the agent <i>in vivo</i> .
Zhao H, 2013 ¹³⁰	FF down-regulates the expressions of androgen receptor (AR) and AR target genes and induces oxidative stress in the prostate cancer cell line LNCaP.

Table 12. Other anticancer activities: increased/decreased radiation sensitivity.

Reference	FF activities
Liu Z, 2012 ¹³¹	FF can reduce radiation sensitivity by ROS scavenging via SOD induction in HeLa. SOD induction by FF is related with PPAR α .
Ge Y, 2014 ¹³²	FF enhances radiosensitivity of esophageal squamous cell carcinoma by suppressing hypoxia-inducible factor-1 α expression.
Liu J, 2014 ¹³³	FF enhances radiosensitivity of HNSCC by inducing arrest and apoptosis.

Table 13. FF and semaphorin-6B down-regulation.

Collet P, 2004 ¹³⁴	Established that PPAR α activators (clofibrate) diminished the expression of the human SEMA6B gene. Expression of SEMA6B gene in human glioblastoma T98G cells was down-regulated with clofibrate.
Murad H, 2006 ¹³⁵	Treatments with FF and troglitazone (a PPAR γ ligand) strongly decreased the Sema6B mRNA. The drop in Sema6B mRNA level and in protein content was more important when the treatment combined the action of FF or troglitazone and 9-cis-retinoic acid.

Table 14. Other miscellaneous anti-cancer activities.

Reference	FF activities
Murakami H, 2006 ¹³⁸	FF activates AMPK and increases eNOS phosphorylation in HUVEC cells without transcriptional activity.
Jiying W, 2012 ¹³⁹	Combined arsenic trioxide and FF exert a significant effect on epithelial-mesenchymal transformation of A549 cells, which may be related with the expression of E-cadherin and Snail.

Table 15. Cancer prevention.

Reference	PPAR α agonists activities
Tuillier P, 2000 ⁵⁶	PPAR α agonists partially prevent tumor development in skin induced carcinogenesis.
Tanaka T, 2001 ¹⁴⁰	PPAR α agonists prevent abnormal crypt foci in induced colon cancer.

FF was tested in different tumor cell lines. Table 16 summarizes this research.

HIV treatment with protease inhibitors has a frequent side effect: lipodystrophy syndrome. FF has been very effective in the treatment of this syndrome¹⁴². Nelfinavir and ritonavir are protease inhibitors which have shown many anti-cancer activities. We have postulated nelfinavir as a complementary off target treatment for cancer¹⁴³. The association of FF with nelfinavir may prevent lipodystrophy, hypertriglyceridemia and elevation of lipoparticles^{144–146}. There is no experimental proof of synergy of this interaction regarding cancer treatment, but both drugs share certain characteristics that make synergy a very plausible feature.

Nelfinavir is a proteasome inhibitor, and proteasome is the site where PPAR α is disassembled, so nelfinavir should prolong PPAR α 's life. Moreover nelfinavir and FF share the following activities: Akt inhibition, anti-angiogenesis, decreased proliferation, increased apoptosis, reduction of MMP2 and MMP9, and increased p21¹⁴³.

Table 17 shows similarities and differences between nelfinavir and FF. The main purpose of this table is to illustrate the similarities and differences between these two drugs regarding cancer: nelfinavir down-regulates CDK-2 and FF down-regulates cyclin D-1 reinforcing cell cycle slowdown. Both are strong anti-angiogenic agents. FF also down-regulates COX2 which is an important step in decreasing angiogenesis.

Discussion

PPAR α is highly expressed in certain cancer cells like endometrium²⁶, prostate¹⁴⁷, bladder¹⁴⁸, certain breast cancer cell lines¹⁴⁹, NSCLC¹⁵¹ and others.

In these cases, the administration of a PPAR α agonist like FF increased apoptosis and decreased proliferation.

In human breast cancer cell lines MCF-7 and MDA-MB-231, PPAR α was overexpressed but use of agonists of this receptor increased proliferation¹⁴⁹.

In stark contrast, Li *et al.*¹⁵¹ tested FF in 12 breast cancer cell lines (including MDA-MB-231) and in all of them FF was effective as proliferation inhibitor. This effectiveness was independent of PPAR α expression but was linked to triple negative condition. Paradoxically MDA-MB-231 was the more sensitive to inhibition of proliferation by FF treatment.

In human colon cancer tissues PPAR α is underexpressed when compared with normal tissues¹⁵⁰. Using PPAR α ligands in APC^{Min/+} mice to evaluate polyp formation, those treated showed decreased number of polyps and decreased size. We may conclude that overexpression or under-expression of PPAR α in cancer tissues is not an indicator of future response to FF or other PPAR α agonists.

Another issue to consider is the species-specific response to PPAR α agonists: for instance, FF induces hepatocarcinogenesis in rodents but not in humans, insulin resistance in mouse but not in humans, oxidative stress in mouse heart but not in human heart. Human liver has a lower expression of PPAR α than rodents¹⁵² (The differences of PPAR α in human liver has been extensively described in the review by Roberts¹⁵³).

There are important differences between rat and human hepatic cells. Vanden Heuvel *et al.*¹⁵⁴ studied the gene expression differences

Table 16. Experience with FF in different tumor cell lines.

REFERENCE	TUMOR CELL LINE	SPECIE
Panigraphy, 2008 ²¹	MELANOMA	mice
Huang, 2013 ⁶²	MELANOMA	human
Grabacka M, 2006 ⁷⁹	MELANOMA	human and mouse
Wilk A, 2015 ⁸⁸	GLIOBLASTOMA	mouse
Han DF, 2015 ¹⁵⁸	GLIOBLASTOMA	human
Binello E, 2014 ⁴¹	GLIOBLASTOMA	human
Wilk A, 2012 ¹⁵⁶	GLIOBLASTOMA	human
Drukala, 2010 ¹²⁸	GLIOBLASTOMA	human
Urbanska, 2008 ¹²⁷	MEDULLOBLASTOMA	mouse and human
Piowarczyk, 2015 ⁶²	PROSTATE CARCINOMA	human
Zhao H, 2013 ¹³⁰	PROSTATE CARCINOMA	human
Wybieralska E, 2011 ¹⁰⁷	PROSTATE CARCINOMA	human
Li T, 2014 ⁴⁰	BREAST CANCER (triple negative)	human
Kuno T, 2014 ⁸¹	LUNG CANCER	mice
Liang H, 2014 ⁶⁴	LUNG CANCER	human

Table 17. Similarities and differences between nelfinavir and FF.

	NELFINAVIR	FENOFIBRATE
NF-kB	Down-regulates	Down-regulates
MMP-2 and 9	Down-regulates	Down-regulates
CDK-2	Down-regulates	
Cyclin D-1		Down-regulates
VEGF	Down-regulates	Down-regulates
HIF-1	Down-regulates	Down-regulates
bFGF	Down-regulates	Down-regulates
COX-2		Down-regulates
FAS	Down-regulates	Down-regulates
AKT inhibition	Strong inhibitor	Inhibitor in certain tissues
AMPK		Activator
Radiosensitivity	Increases	Increases
ER stressor	Stressor	
Growth	Slows down	Slows down
Angiogenesis	Decreases	Decreases
Invasion	Decreases	Decreases
nSREBP-1	Inhibits	Does not inhibit
SREBP-2		Inhibitor
Apoptosis	Increases	Increases
Breast cancer resistance protein	Inhibits	
ATP mitochondrial production	Decreases	Decreases
Adhesion molecules		Down-regulates
Lipodistrophy	Produces lypodistrophy	Prevents lipodistrophy
Triglycerides	Increases	Decreases
Androgen receptor	Down-regulates	Down-regulates

Note: Gray rectangle means that the activity has not been checked or has not been published.

between rat hepatoma cells (FaO) and human hepatocarcinoma cells (HepG2) when treated with a PPAR α agonist like WY14643. A large number of kinases and phosphatases were affected in FaO and not in HepG2 cells. Many of them were implicated in cell cycle control and growth signaling like JAK1, JAK2, GSK3 α and MKP-1.

Rat peroxisomes contain urate oxidase which is absent in human peroxisomes¹⁵⁵.

Acyl Co A oxidase (ACO) is a key enzyme in peroxisomes and according to Roberts *et al.*¹⁵³ there are differences between human and rat ACO: the promoter for human ACO has a different sequence and activity from rats ACO.

PPAR α agonists like FF are tissue-specific. They may increase VEGF and angiogenesis in retina^{22,23} and the opposite in tumor cells^{20,21}.

Thus this species- and tissue-specificity suggests that we should be cautious when interpreting the results of many of the published investigations. PPAR α agonists research results obtained in rodents should not be taken for granted in humans.

The mechanism of FF anticancer activity may differ in different tumors: in mantle cell lymphoma it seems to induce apoptosis by inhibiting the TNF α /NF-kB axis³⁸ while in triple negative breast cancer it requires activation of NF-kB in order to induce apoptosis⁴⁰.

PPAR α agonists like FF are actively investigated as anti-cancer drugs, but paradoxically, PPAR α inhibitors may also work against cancer. This is the case of renal cell carcinoma⁴⁵ where an inhibitor of this receptor produced cell cycle arrest and apoptosis.

After these necessary clarifying precautions, we must consider in detail the hard evidence collected in the medical literature that gives

ground for FF as a complementary adjunct pharmaceutical in cancer therapy.

Phanigraphy *et al.*²¹ tested 19 human tumor cell lines *in vitro* and found that all expressed PPAR α in tumor cells and endothelium. There were differences regarding levels of PPAR α . Fibrates and particularly FF at clinically achievable concentrations showed capacity to inhibit proliferation in these cell lines that included highly malignant ones like melanoma and Lewis lung carcinoma cell lines. FF inhibited 95% of bovine capillary endothelial cells proliferation and migration. There was no inhibition on normal fibroblasts growth. In glioblastoma cells FF reduced VEGF secretion by 50% and increased TSP-1 expression by 3- to 4- fold in a fibrosarcoma cell line. The results of these experiments show that FF exerts anti-proliferative and anti-angiogenic activities in tumor cells *in vitro* at clinically achievable concentrations. Similar results were observed in subcutaneously implanted tumors in mice. The seminal work of Panigraphy *et al.* concludes that anti-proliferative and anti-angiogenic properties of FF are PPAR α activation dependent.

Glioblastoma treatment has already introduced FF as part of different anti-angiogenic schedules, but FF may have also other anti-tumoral effects in this disease besides anti-angiogenesis, particularly apoptosis^{156–158}.

Endometrial carcinoma usually overexpresses PPAR α . When PPAR α expression is reduced with siRNA *in vitro*, cellular proliferation decreased substantially and showed a small increase in apoptosis in Ishikawa cells and HEC-1A cells²⁷. Both cell lines reduced VEGF levels when they were treated with FF. Reduction in VEGF after FF treatment showed differences between the two cell lines: HEC-1A showed potentiation of inhibition of VEGF when an RXR ligand was added; Ishikawa cells did not. This reinforces the concept that there may appear important differences with FF treatment according to the tumor type.

FF also uses the AMPK pathway to produce its anti-tumoral effects¹⁵⁹. This is a PPAR α independent action that has been demonstrated in human oral squamous cell carcinoma (OSCC) where FF inhibited cell migration and invasion and reduced expression of MMP 1, 2, 7 and 9. LKB1 and AMPK were up-regulated after FF treatment. When AMPK was inhibited (with protein C) the anti-invasive effect was significantly reduced.

Metformin is another activator of the AMPK pathway. It has not been tested with FF but it is quite possible that there might be synergy in

this activity. Another coincidence between metformin and FF is the decrease in cellular energy production.

The molecular mechanism of many of the FF anti-cancer activities is known since 2006¹⁶⁰ and can be summarized as inhibition of COX2 and VEGF at the transcription level by interfering with AP-1 binding to DNA and decreased expression of NF- κ B. In susceptible cells there is a negative cross talk between PPAR α and AP-1¹⁶⁰.

Another mechanism postulated in anti-cancer activity is the disruption of the tumor-host stroma symbiosis due to anti-angiogenesis and anti-inflammatory activity¹⁶¹.

Finally we have to mention that FF effectively reduces nuclear SREBP-2 but not SREBP-1^{162–165}. Nelfinavir and PUFA inhibit mature SREB-1 which is a transcription factor that promotes FAS synthesis, so these products may complement FF anti-cancer activity.

Conclusion

As observed in the tables, FF exerts polyvalent anti-cancer activities that deserve further research in the clinical setting.

FF is a PPAR α agonist drug developed for treatment of elevated triglycerides and LDL cholesterol reducing cardiovascular risk that may be repurposed to be used in cancer due to its anti-angiogenic, anti-inflammatory, anti-proliferative, anti-metastatic, anti-adhesive, anti-invasive and pro-apoptotic activities in certain cancers.

Future perspectives

FF has already been incorporated in anti-angiogenic protocols for the treatment of glioblastoma. Probably in the future it will form part of protocols based on repurposed drugs directed to inhibit angiogenesis like celecoxib, nelfinavir, and metformin.

Colorectal and prostate cancer seem good candidates for these therapies.

Competing interests

No competing interests were disclosed.

Grant information

The author(s) declared that no grants were involved in supporting this work.

References

1. Yang LP, Keating GM: **Fenofibric acid: in combination therapy in the treatment of mixed dyslipidemia.** *Am J Cardiovasc Drugs.* 2009; **9**(6): 401–409.
[PubMed Abstract](#) | [Publisher Full Text](#)
2. Staels B, Vu-Dac N, Kosykh VA, *et al.*: **Fibrates downregulate apolipoprotein C-III expression independent of induction of peroxisomal acyl coenzyme A oxidase. A potential mechanism for the hypolipidemic action of fibrates.** *J Clin Invest.* 1995; **95**(2): 705–12.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
3. Marx N, Sukhova GK, Collins T, *et al.*: **PPARalpha activators inhibit cytokine-induced vascular cell adhesion molecule-1 expression in human endothelial cells.** *Circulation.* 1999; **99**(24): 3125–3131.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
4. Shu H, Wong B, Zhou G, *et al.*: **Activation of PPARalpha or gamma reduces secretion of matrix metalloproteinase 9 but not interleukin 8 from human monocytic THP-1 cells.** *Biochem Biophys Res Commun.* 2000; **267**(1): 345–349.
[PubMed Abstract](#) | [Publisher Full Text](#)

5. Rival Y, Benéteau N, Taillandier T, *et al.*: **PPARalpha and PPARdelta activators inhibit cytokine-induced nuclear translocation of NF-kappaB and expression of VCAM-1 in EAhy926 endothelial cells.** *Eur J Pharmacol.* 2002; **435**(2–3): 143–51.
[PubMed Abstract](#) | [Publisher Full Text](#)
6. Goetze S, Eilers F, Bungenstock A, *et al.*: **PPAR activators inhibit endothelial cell migration by targeting Akt.** *Biochem Biophys Res Commun.* 2002; **293**(5): 1431–7.
[PubMed Abstract](#) | [Publisher Full Text](#)
7. Jiao HL, Zhao BL: **Cytotoxic effect of peroxisome proliferator fenofibrate on human HepG2 hepatoma cell line and relevant mechanisms.** *Toxicol Appl Pharmacol.* 2002; **185**(3): 172–9.
[PubMed Abstract](#) | [Publisher Full Text](#)
8. Varet J, Vincent L, Mirshahi P, *et al.*: **Fenofibrate inhibits angiogenesis *in vitro* and *in vivo*.** *Cell Mol Life Sci.* 2003; **60**(4): 810–9.
[PubMed Abstract](#) | [Publisher Full Text](#)
9. Lu Y, Cai Z, Galsion DL, *et al.*: **Monocyte chemotactic protein-1 (MCP-1) acts as a paracrine and autocrine factor for prostate cancer growth and invasion.** *Prostate.* 2006; **66**(12): 1311–1318.
[PubMed Abstract](#) | [Publisher Full Text](#)
10. Sonoki K, Iwase M, Iino K, *et al.*: **Dilazep and fenofibric acid inhibit MCP-1 mRNA expression in glycoxidized LDL-stimulated human endothelial cells.** *Eur J Pharmacol.* 2003; **475**(1–3): 139–147.
[PubMed Abstract](#) | [Publisher Full Text](#)
11. Meissner M, Stein M, Urbich C, *et al.*: **PPARalpha activators inhibit vascular endothelial growth factor receptor-2 expression by repressing Sp1-dependent DNA binding and transactivation.** *Circ Res.* 2004; **94**(3): 324–332.
[PubMed Abstract](#) | [Publisher Full Text](#)
12. Empen K, Frost RJ, Geiss HC, *et al.*: **Differential effects of fenofibrate versus atorvastatin on the concentrations of E-selectin and vascular cellular adhesion molecule-1 in patients with type 2 diabetes mellitus and mixed hyperlipoproteinemia: a randomized cross-over trial.** *Cardiovasc Diabetol.* 2003; **2**: 17.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
13. Holland CM, Saidi SA, Evans AL, *et al.*: **Transcriptome analysis of endometrial cancer identifies peroxisome proliferator-activated receptors as potential therapeutic targets.** *Mol Cancer Ther.* 2004; **3**(8): 993–1001.
[PubMed Abstract](#)
14. Grabacka M, Placha W, Plonka PM, *et al.*: **Inhibition of melanoma metastases by fenofibrate.** *Arch Dermatol Res.* 2004; **296**(2): 54–8.
[PubMed Abstract](#) | [Publisher Full Text](#)
15. Gunin AG, Bitter AD, Demakov AB, *et al.*: **Effects of peroxisome proliferator activated receptors-alpha and -gamma agonists on estradiol-induced proliferation and hyperplasia formation in the mouse uterus.** *J Endocrinol.* 2004; **182**(2): 229–39.
[PubMed Abstract](#) | [Publisher Full Text](#)
16. Kubota T, Yano T, Fujisaki K, *et al.*: **Fenofibrate induces apoptotic injury in cultured human hepatocytes by inhibiting phosphorylation of Akt.** *Apoptosis.* 2005; **10**(2): 349–358.
[PubMed Abstract](#) | [Publisher Full Text](#)
17. Okopień B, Kowalski J, Krysiak R, *et al.*: **Monocyte suppressing action of fenofibrate.** *Pharmacol Rep.* 2005; **57**(3): 367–72.
[PubMed Abstract](#)
18. Okamoto H, Iwamoto T, Kotake S, *et al.*: **Inhibition of NF-kappaB signaling by fenofibrate, a peroxisome proliferator-activated receptor-alpha ligand, presents a therapeutic strategy for rheumatoid arthritis.** *Clin Exp Rheumatol.* 2005; **23**(3): 323–30.
[PubMed Abstract](#)
19. Blann AD, Belgore FM, Constans J, *et al.*: **Plasma vascular endothelial growth factor and its receptor Flt-1 in patients with hyperlipidemia and atherosclerosis and the effects of fluvastatin or fenofibrate.** *Am J Cardiol.* 2001; **87**(10): 1160–1163.
[PubMed Abstract](#) | [Publisher Full Text](#)
20. Pozzi A, Popescu V, Yang S, *et al.*: **The anti-tumorigenic properties of peroxisomal proliferator-activated receptor alpha are arachidonic acid epoxidase-mediated.** *J Biol Chem.* 2010; **285**(17): 12840–12850.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
21. Panigraphy D, Kaipainen A, Huang S, *et al.*: **PPARalpha agonist fenofibrate suppresses tumor growth through direct and indirect angiogenesis inhibition.** *Proc Natl Acad Sci U S A.* 2008; **105**(3): 985–990.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
22. Zhou J, Zhang S, Xue J, *et al.*: **Activation of peroxisome proliferator-activated receptor α (PPAR α) suppresses hypoxia-inducible factor-1 α (HIF-1 α) signaling in cancer cells.** *J Biol Chem.* 2012; **287**(42): 35161–35169.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
23. Dana N, Javanmard SH, Fazilati M, *et al.*: **A comparison of peroxisome proliferator-activated receptor- α agonist and antagonist on human umbilical vein endothelial cells angiogenesis.** *Adv Biomed Res.* 2013; **2**: 54.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
24. Kim J, Ahn JH, Kim JH, *et al.*: **Fenofibrate regulates retinal endothelial cell survival through the AMPK signal transduction pathway.** *Exp Eye Res.* 2007; **84**(5): 886–893.
[PubMed Abstract](#) | [Publisher Full Text](#)
25. Chew EY, Ambrosius WT, Davis MD, *et al.*: **Effects of medical therapies on retinopathy progression in type 2 diabetes.** *N Engl J Med.* 2010; **363**(3): 233–244.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
26. Noonan JE, Jenkins AJ, Ma JX, *et al.*: **An update on the molecular actions of Fenofibrate and its clinical effects on diabetic retinopathy and other microvascular end points in patients with diabetes.** *Diabetes.* 2013; **62**(12): 3968–3975.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
27. Nickkho-Amiry M, McVey R, Holland C: **Peroxisome proliferator-activated receptors modulate proliferation and angiogenesis in human endometrial Carcinoma.** *Mol Cancer Res.* 2012; **10**(3): 441–453.
[PubMed Abstract](#) | [Publisher Full Text](#)
28. Onalan G, Zeyneloglu HB, Bayraktar N: **Fenofibrate causes regression of endometriotic implants: a rat model.** *Fertil Steril.* 2009; **92**(6): 2100–2102.
[PubMed Abstract](#) | [Publisher Full Text](#)
29. Robison NJ, Campigotto F, Chi SN, *et al.*: **A phase II trial of a multi-agent oral antiangiogenic (metronomic) regimen in children with recurrent or progressive cancer.** *Pediatr Blood Cancer.* 2014; **61**(4): 636–642.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
30. Peyrl A, Chocholous M, Kieran MW, *et al.*: **Antiangiogenic metronomic therapy for children with recurrent embryonal brain tumors.** *Pediatr Blood Cancer.* 2012; **59**(3): 511–517.
[PubMed Abstract](#) | [Publisher Full Text](#)
31. Peyrl A, Chocholous M, Kieran MW, *et al.*: **Metronomic antiangiogenic therapy in children with recurrent brain tumours of different histologies.** *Magazine of European Medical Oncology.* 2011; **4**(3): 21–23.
[Publisher Full Text](#)
32. Sterba J, Pavelka Z, Andre N, *et al.*: **Second complete remission of relapsed medulloblastoma induced by metronomic chemotherapy.** *Pediatr Blood Cancer.* 2010; **54**(4): 616–617.
[PubMed Abstract](#) | [Publisher Full Text](#)
33. Zapletalova D, André N, Deak L, *et al.*: **Metronomic chemotherapy with the COMBAT regimen in advanced pediatric malignancies: a multicenter experience.** *Oncology.* 2012; **82**(5): 249–260.
[PubMed Abstract](#)
34. Pozzi A, Ibanez MR, Gatica AE, *et al.*: **Peroxisomal proliferator-activated receptor-alpha-dependent inhibition of endothelial cell proliferation and tumorigenesis.** *J Biol Chem.* 2007; **282**(24): 17685–17695.
[PubMed Abstract](#) | [Publisher Full Text](#)
35. Pozzi A, Capdevila JH: **PPARalpha Ligands as Antitumorigenic and Antiangiogenic Agents.** *PPAR Res.* 2008; **2008**: 906542.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
36. Avis I, Hong SH, Martinez A, *et al.*: **Five-lipoxygenase inhibitors can mediate apoptosis in human breast cancer cell lines through complex eicosanoid interactions.** *FASEB J.* 2001; **15**(11): 2007–9.
[PubMed Abstract](#) | [Publisher Full Text](#)
37. Chinetti G, Griglio S, Antonucci M, *et al.*: **Activation of proliferator-activated Receptors alpha and gamma induces apoptosis of human monocyte-derived macrophages.** *J Biol Chem.* 1998; **273**(40): 25573–25580.
[PubMed Abstract](#) | [Publisher Full Text](#)
38. Zak Z, Gelebart P, Lai R: **Fenofibrate induces effective apoptosis in mantle cell lymphoma by inhibiting the TNFalpha/NF-kappaB signaling axis.** *Leukemia.* 2010; **24**(8): 1476–1486.
[PubMed Abstract](#) | [Publisher Full Text](#)
39. Wang J, Wang T, Zeng J, *et al.*: **Experimental study of fenofibrate combined with cisplatin on inhibition and apoptosis of human lung cancer A549 cell line.** *Shandong Medical Journal.* 2011; **48**.
[Reference Source](#)
40. Li T, Zhang Q, Zhang J, *et al.*: **Fenofibrate induces apoptosis of triple-negative breast cancer cells via activation of NF- κ B pathway.** *BMC Cancer.* 2014; **14**: 96.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
41. Binello E, Mormone E, Emdad L, *et al.*: **Characterization of fenofibrate-mediated anti-proliferative pro-apoptotic effects on high-grade gliomas and anti-invasive effects on glioma stem cells.** *J Neurooncol.* 2014; **117**(2): 225–234.
[PubMed Abstract](#) | [Publisher Full Text](#)
42. Majeed Y, Taba T, Shaheen Y: **Molecular basis of the anti-proliferative action of the hypolipidemic drug fenofibrate *in vitro* in angiosarcoma-forming endothelial cells.** *Qatar Foundation Annual Research Conference Proceedings Volume 1 HBPP0064.* 2014.
[Reference Source](#)
43. Penna F, Pin F, Costamagna D, *et al.*: **Caspase 2 activation and ER stress drive rapid Jurkat cell apoptosis by clofibrate.** *PLoS One.* 2012; **7**(9): e45327.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
44. Penna F, Reffo P, Muzio G, *et al.*: **Mechanisms of clofibrate-induced apoptosis in Yoshida AH-130 hepatoma cells.** *Biochem Pharmacol.* 2009; **77**(2): 169–176.
[PubMed Abstract](#) | [Publisher Full Text](#)
45. Abu Aboud O, Wettersten HI, Weiss RH: **Inhibition of PPAR α induces cell cycle arrest and apoptosis, and synergizes with glycolysis inhibition in kidney cancer cells.** *PLoS One.* 2013; **8**(8): e71115.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)

46. Pascal M, Sepulchre C, Chazan JB, *et al.*: Evidence for the inhibition of platelet-derived growth factor induced rat smooth muscle cells DNA synthesis by fenofibric acid at the Go/G₁ cell cycle level. *Life Sci.* 1983; 33(10): 925–33. [PubMed Abstract](#) | [Publisher Full Text](#)
47. Munro E, Patel M, Chan P, *et al.*: Growth inhibition of human vascular smooth muscle cells by fenofibrate: a possible therapy for restenosis. *Cardiovasc Res.* 1994; 28(5): 615–20. [PubMed Abstract](#) | [Publisher Full Text](#)
48. Zeng R, Xiong Y, Zhu F, *et al.*: Fenofibrate attenuated glucose-induced mesangial cells proliferation and extracellular matrix synthesis via PI3K/AKT and ERK1/2. *PLoS One.* 2013; 8(10): e76836. [PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
49. Song Q, Sun J, Wang J, *et al.*: [Role of TRB3 in the inhibitory effect of fenofibrate against high glucose-induced proliferation of glomerular mesangial cells]. *Nan Fang Yi Ke Da Xue Xue Bao.* 2013; 33(3): 391–6. [PubMed Abstract](#) | [Publisher Full Text](#)
50. Selim E, Frkanec JT, Cunard R: Fibrates upregulate TRB3 in lymphocytes independent of PPAR alpha by augmenting CCAAT/enhancer-binding protein beta (C/EBP beta) expression. *Mol Immunol.* 2007; 44(6): 1218–1229. [PubMed Abstract](#) | [Publisher Full Text](#)
51. Morse E, Selim E, Cunard R: PPARalpha ligands cause lymphocyte depletion and cell cycle block and this is associated with augmented TRB3 and reduced Cyclin B1 expression. *Mol Immunol.* 2009; 46(16): 3454–3461. [PubMed Abstract](#) | [Publisher Full Text](#)
52. Ogata T, Miyauchi T, Irukayama-Tomobe Y, *et al.*: The peroxisome proliferator-activated receptor alpha activator fenofibrate inhibits endothelin-1-induced cardiac fibroblast proliferation. *J Cardiovasc Pharmacol.* 2004; 44(Suppl 1): S279–82. [PubMed Abstract](#) | [Publisher Full Text](#)
53. Irukayama-Tomobe Y, Miyauchi T, Sakai S, *et al.*: Endothelin-1-induced cardiac hypertrophy is inhibited by activation of peroxisome proliferator-activated receptor-alpha partly via blockade of c-Jun NH2-terminal kinase pathway. *Circulation.* 2004; 109(7): 904–910. [PubMed Abstract](#) | [Publisher Full Text](#)
54. Irukayama-Tomobe Y, Miyauchi T, Kasuya Y, *et al.*: Activation of peroxisome proliferator-activated receptor-alpha decreases endothelin-1-induced p38 mitogen-activated protein kinase activation in cardiomyocytes. *J Cardiovasc Pharmacol.* 2004; 44(Suppl 1): S358–61. [PubMed Abstract](#) | [Publisher Full Text](#)
55. Lee JK, Seo EM, Lee SS, *et al.*: Activation of PPARalpha Attenuates IFNgamma and IL-1beta-induced Cell Proliferation in Astrocytes: Involvement of IL-6 Independent Pathway. *Korean J Physiol Pharmacol.* 2010; 14(3): 185–9. [PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
56. Thuillier P, Anchiraco GJ, Nickel KP, *et al.*: Activators of peroxisome proliferator-activated receptor-alpha partially inhibit mouse skin tumor promotion. *Mol Carcinog.* 2000; 29(3): 134–142. [PubMed Abstract](#) | [Publisher Full Text](#)
57. Gizard F, Amant C, Barbier O, *et al.*: PPAR alpha inhibits vascular smooth muscle cell proliferation underlying intimal hyperplasia by inducing the tumor suppressor p16^{INK4a}. *J Clin Invest.* 2005; 115(11): 3228–3238. [PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
58. Saidi SA, Holland CM, Charnock-Jones DS, *et al.*: In vitro and in vivo effects of the PPAR-alpha agonists fenofibrate and retinoic acid in endometrial cancer. *Mol Cancer.* 2006; 5: 13. [PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
59. Yokoyama Y, Xin B, Shigeto T, *et al.*: Clofibrate acid, a peroxisome proliferator-activated receptor alpha ligand, inhibits growth of human ovarian cancer. *Mol Cancer Ther.* 2007; 6(4): 1379–86. [PubMed Abstract](#) | [Publisher Full Text](#)
60. Yamasaki D, Kawabe N, Nakamura H, *et al.*: Fenofibrate suppresses growth of the human hepatocellular carcinoma cell via PPARα-independent mechanisms. *Eur J Cell Biol.* 2011; 90(8): 657–64. [PubMed Abstract](#) | [Publisher Full Text](#)
61. Chang NW, Tsai MH, Lin C, *et al.*: Fenofibrate exhibits a high potential to suppress the formation of squamous cell carcinoma in an oral-specific 4-nitroquinoline 1-oxide/arecoline mouse model. *Biochim Biophys Acta.* 2011; 1812(4): 558–64. [PubMed Abstract](#) | [Publisher Full Text](#)
62. Huang J, Das SK, Jha P, *et al.*: The PPARα agonist fenofibrate suppresses B-cell lymphoma in mice by modulating lipid metabolism. *Biochim Biophys Acta.* 2013; 1831(10): 1555–1565. [PubMed Abstract](#) | [Publisher Full Text](#)
63. Wang H, He CH, Bai LP, *et al.*: [Effects of fenofibrate on the growth and migration of ovarian cancer cells in vitro]. *Sichuan Da Xue Xue Bao Yi Xue Ban.* 2014; 45(5): 789–92. [PubMed Abstract](#)
64. Liang H, Kowalczyk P, Junco JJ, *et al.*: Differential effects on lung cancer cell proliferation by agonists of glucocorticoid and PPARα receptors. *Mol Carcinog.* 2014; 53(9): 753–763. [PubMed Abstract](#) | [Publisher Full Text](#)
65. Zhang C, Beckermann B, Kalifatidis G, *et al.*: Corticosteroids induce chemotherapy resistance in the majority of tumour cells from bone, brain, breast, cervix, melanoma and neuroblastoma. *Int J Oncol.* 2006; 29(5): 1295–1301. [PubMed Abstract](#) | [Publisher Full Text](#)
66. Beg AA, Baltimore D: An essential role for NF-kappaB in preventing TNF-alfa-induced cell death. *Science.* 1996; 274(5288): 782–784. [PubMed Abstract](#) | [Publisher Full Text](#)
67. Van Antwerp DJ, Martin SJ, Kafri T, *et al.*: Suppression of TNF-alpha induced apoptosis by NF-kappaB. *Science.* 1996; 274(5288): 787–789. [PubMed Abstract](#) | [Publisher Full Text](#)
68. Wang CY, Mayo MW, Baldwin AS Jr: TNF- and cancer therapy-induced apoptosis: potentiation by inhibition of NF-kappaB. *Science.* 1996; 274(5288): 784–787. [PubMed Abstract](#) | [Publisher Full Text](#)
69. Baldwin AS: Control of oncogenesis and cancer therapy resistance by the transcription factor NF-kappaB. *J Clin Invest.* 2001; 107(3): 241–246. [PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
70. Staels B, Koenig W, Habib A, *et al.*: Activation of human aortic smooth-muscle cells is inhibited by PPARalpha but not by PPARgamma activators. *Nature.* 1998; 393(6687): 790–3. [PubMed Abstract](#) | [Publisher Full Text](#)
71. Xu X, Otsuki M, Saito H, *et al.*: PPARalpha and GR differentially down-regulate the expression of nuclear factor-kappaB-responsive genes in vascular endothelial cells. *Endocrinology.* 2001; 142(8): 3332–9. [PubMed Abstract](#) | [Publisher Full Text](#)
72. Ogata T, Miyauchi T, Sakai S, *et al.*: Myocardial fibrosis and diastolic dysfunction in deoxycorticosterone acetate-salt hypertensive rats is ameliorated by the peroxisome proliferator-activated receptor-alpha activator fenofibrate, partly by suppressing inflammatory responses associated with the nuclear factor-kappa-B pathway. *J Am Coll Cardiol.* 2004; 43(8): 1481–1488. [PubMed Abstract](#) | [Publisher Full Text](#)
73. Yang TL, Chen MF, Luo BL, *et al.*: Fenofibrate decreases asymmetric dimethylarginine level in cultured endothelial cells by inhibiting NF-kappaB activity. *Naunyn Schmiedeberg's Arch Pharmacol.* 2005; 371(5): 401–7. [PubMed Abstract](#) | [Publisher Full Text](#)
74. Xu J, Chavis JA, Racke MK, *et al.*: Peroxisome proliferator-activated receptor-alpha and retinoid X receptor agonists inhibit inflammatory responses of astrocytes. *J Neuroimmunol.* 2006; 176(1–2): 95–105. [PubMed Abstract](#) | [Publisher Full Text](#)
75. Li L, Emmett N, Mann D, *et al.*: Fenofibrate attenuates tubulointerstitial fibrosis and inflammation through suppression of nuclear factor-κB and transforming growth factor-β1/Smad3 in diabetic nephropathy. *Exp Biol Med (Maywood).* 2010; 235(3): 383–91. [PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
76. Yang CS, Yuk JM, Kim JJ, *et al.*: Small heterodimer partner-targeting therapy inhibits systemic inflammatory responses through mitochondrial uncoupling protein 2. *PLoS One.* 2013; 8(5): e63435. [PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
77. Shen W, Gao Y, Lu B, *et al.*: Negatively regulating TLR4/NF-κB signaling via PPARα in endotoxin-induced uveitis. *Biochim Biophys Acta.* 2014; 1842(7): 1109–20. [PubMed Abstract](#) | [Publisher Full Text](#)
78. Binello E, Germano IM: Targeting glioma stem cells: a novel framework for brain tumors. *Cancer Sci.* 2011; 102(11): 1958–66. [PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
79. Grabacka M, Plonka PM, Urbanska K, *et al.*: Peroxisome proliferator-activated receptor alpha activation decreases metastatic potential of melanoma cells in vitro via down-regulation of Akt. *Clin Cancer Res.* 2006; 12(10): 3028–36. [PubMed Abstract](#) | [Publisher Full Text](#)
80. Li R, Zheng W, Pi R, *et al.*: Activation of peroxisome proliferator-activated receptor-alpha prevents glycogen synthase 3beta phosphorylation and inhibits cardiac hypertrophy. *FEBS Lett.* 2007; 581(17): 3311–6. [PubMed Abstract](#) | [Publisher Full Text](#)
81. Kuno T, Hata K, Takamatsu M, *et al.*: The peroxisome proliferator-activated receptor (PPAR) α agonist fenofibrate suppresses chemically induced lung alveolar proliferative lesions in male obese hyperlipidemic mice. *Int J Mol Sci.* 2014; 15(5): 9160–72. [PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
82. Piwowarczyk K, Wybieralska E, Baran J, *et al.*: Fenofibrate enhances barrier function of endothelial continuum within the metastatic niche of prostate cancer cells. *Expert Opin Ther Targets.* 2015; 19(2): 163–76. [PubMed Abstract](#) | [Publisher Full Text](#)
83. Keller BJ, Yamanaka H, Thurman RG: Inhibition of mitochondrial respiration and oxygen-dependent hepatotoxicity by six structurally dissimilar peroxisomal proliferating agents. *Toxicology.* 1992; 71(1–2): 49–61. [PubMed Abstract](#) | [Publisher Full Text](#)
84. Zhou Z, Wallace KB: The effect of peroxisome proliferators on mitochondrial bioenergetics. *Toxicol Sci.* 1999; 48(1): 82–89. [PubMed Abstract](#) | [Publisher Full Text](#)
85. Casas F, Pineau T, Rochard P, *et al.*: New molecular aspects of regulation of mitochondrial activity by fenofibrate and fasting. *FEBS Lett.* 2000; 482(1–2): 71–4. [PubMed Abstract](#) | [Publisher Full Text](#)
86. Brunmair B, Lest A, Staniek K, *et al.*: Fenofibrate impairs rat mitochondrial function by inhibition of respiratory complex I. *J Pharmacol Exp Ther.* 2004; 311(1): 109–114. [PubMed Abstract](#) | [Publisher Full Text](#)

87. Nadanaciva S, Dykens JA, Bernal A, *et al.*: Mitochondrial impairment by PPAR agonists and statins identified via immunocaptured OXPHOS complex activities and respiration. *Toxicol Appl Pharmacol.* 2007; **223**(3): 277–287. [PubMed Abstract](#) | [Publisher Full Text](#)
88. Wilk AM, Urbanska K, Impastato D, *et al.*: Abstract 3230: Fenofibrate mediated energy crisis and apoptotic cell death of glioblastoma. *Cancer Res.* 2012; **72**: 3230. [Publisher Full Text](#)
89. Ledesma A, de Lacoba MG, Rial E: The mitochondrial uncoupling proteins. *Genome Biol.* 2002; **3**(12): REVIEWS3015. [PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
90. Finck BN, Kelly DP: Peroxisome proliferator-activated receptor alpha (PPARalpha) signaling in the gene regulatory control of energy metabolism in the normal and diseased heart. *J Mol Cell Cardiol.* 2002; **34**(10): 1249–57. [PubMed Abstract](#) | [Publisher Full Text](#)
91. Pecqueur C, Bui T, Gelly C, *et al.*: Uncoupling protein-2 controls proliferation by promoting fatty acid oxidation and limiting glycolysis-derived pyruvate utilization. *FASEB J.* 2008; **22**(1): 9–18. [PubMed Abstract](#) | [Publisher Full Text](#)
92. Grabacka M, Reiss K: Anticancer Properties of PPARalpha-Effects on Cellular Metabolism and Inflammation. *PPAR Res.* 2008; **2008**: 930705. [PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
93. Srivastava RA, Jahagirdar R, Azhar S, *et al.*: Peroxisome proliferator-activated receptor-alpha selective ligand reduces adiposity, improves insulin sensitivity and inhibits atherosclerosis in LDL receptor-deficient mice. *Mol Cell Biochem.* 2006; **285**(1–2): 35–50. [PubMed Abstract](#) | [Publisher Full Text](#)
94. Baron A, Migita T, Tang D, *et al.*: Fatty acid synthase: a metabolic oncogene in prostate cancer? *J Cell Biochem.* 2004; **91**(1): 47–53. [PubMed Abstract](#) | [Publisher Full Text](#)
95. Hunt DA, Lane HM, Yygmont ME, *et al.*: MRNA stability and overexpression of fatty acid synthase in human breast cancer cell lines. *Anticancer Res.* 2007; **27**(1A): 27–34. [PubMed Abstract](#)
96. Gansler TS, Hardman W 3rd, Hunt DA, *et al.*: Increased expression of fatty acid synthase (OA-519) in ovarian neoplasms predicts shorter survival. *Hum Pathol.* 1997; **28**(6): 686–692. [PubMed Abstract](#) | [Publisher Full Text](#)
97. Camassei FD, Cozza R, Acquaviva A, *et al.*: Expression of the lipogenic enzyme fatty acid synthase (FAS) in retinoblastoma and its correlation with tumor aggressiveness. *Invest Ophthalmol Vis Sci.* 2003; **44**(6): 2399–2403. [PubMed Abstract](#) | [Publisher Full Text](#)
98. Ye Q, Chung LW, Li S, *et al.*: Identification of a novel FAS/ER-alpha fusion transcript expressed in human cancer cells. *Biochim Biophys Acta.* 2000; **1493**(3): 373–377. [PubMed Abstract](#) | [Publisher Full Text](#)
99. Marchesi S, Lupattelli G, Lombardini R, *et al.*: Effects of fenofibrate on endothelial function and cell adhesion molecules during post-prandial lipemia in hypertriglyceridemia. *J Clin Pharm Ther.* 2003; **28**(5): 419–424. [PubMed Abstract](#) | [Publisher Full Text](#)
100. Gervois P, Kleeman R, Pilon A, *et al.*: Global suppression of IL-6-induced acute phase response gene expression after chronic *in vivo* treatment with the peroxisome proliferator-activated receptor-alpha activator fenofibrate. *J Biol Chem.* 2004; **279**: 16154–16160. [PubMed Abstract](#) | [Publisher Full Text](#)
101. Lefebvre P, Chinetti G, Fruchart JC, *et al.*: Sorting out the roles of PPAR alpha in energy metabolism and vascular homeostasis. *J Clin Invest.* 2006; **116**(3): 571–580. [PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
102. Ryan KE, McCance DR, Powell L, *et al.*: Fenofibrate and pioglitazone improve endothelial function and reduce arterial stiffness in obese glucose tolerant men. *Atherosclerosis.* 2007; **194**(2): e123–30. [PubMed Abstract](#) | [Publisher Full Text](#)
103. Rosenson RS, Wolff DA, Huskin AL, *et al.*: Fenofibrate therapy ameliorates fasting and postprandial lipoproteinemia, oxidative stress, and the inflammatory response in subjects with hypertriglyceridemia and the metabolic syndrome. *Diabetes Care.* 2007; **30**(8): 1945–51. [PubMed Abstract](#) | [Publisher Full Text](#)
104. Lee JW, Baiwa PJ, Carson MJ, *et al.*: Fenofibrate represses interleukin-17 and interferon-gamma expression and improves colitis in interleukin-10-deficient mice. *Gastroenterology.* 2007; **133**(1): 108–123. [PubMed Abstract](#) | [Publisher Full Text](#)
105. Li H, Cheng X, Yang X, *et al.*: The effects of fenofibrate on endothelial cell secretion of E-selectin and ICAM-1. *Jiangsu Medical Journal.* 2007; **01**. [Reference Source](#)
106. Samatov TR, Tonevitsky AG, Schumacher U: Epithelial-mesenchymal transition: focus on metastatic cascade, alternative splicing, non-coding RNAs and modulating compounds. *Mol Cancer.* 2013; **12** (1): 107. [PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
107. Wybieralska E, Szpak K, Górecki A, *et al.*: Fenofibrate attenuates contact-stimulated cell motility and gap junctional coupling in DU-145 human prostate cancer cell populations. *Oncol Rep.* 2011; **26**(2): 447–453. [PubMed Abstract](#) | [Publisher Full Text](#)
108. Eberhart CE, Coffey RJ, Radhika A, *et al.*: Up-regulation of cyclooxygenase 2 gene expression in human colorectal adenomas and adenocarcinomas. *Gastroenterology.* 1994; **107**(4): 1183–1188. [PubMed Abstract](#)
109. Elder DJ, Baker JA, Banu NA, *et al.*: Human colorectal adenomas demonstrate a size-dependent increase in epithelial cyclooxygenase-2 expression. *J Pathol.* 2002; **198**(4): 428–434. [PubMed Abstract](#) | [Publisher Full Text](#)
110. Castellone MD, Teramoto H, Williams BO, *et al.*: Prostaglandin E₂ promotes colon cancer cell growth through a G_i-alpha-beta-catenin signaling axis. *Science.* 2005; **310**(5753): 1504–1510. [PubMed Abstract](#) | [Publisher Full Text](#)
111. Bocca C, Ievolella M, Autelli R, *et al.*: Expression of Cox-2 in human breast cancer cells as a critical determinant of epithelial-to-mesenchymal transition and invasiveness. *Expert Opin Ther Targets.* 2014; **18**(2): 121–35. [PubMed Abstract](#) | [Publisher Full Text](#)
112. Kim HS, Moon HG, Han W, *et al.*: COX₂ overexpression is a prognostic marker for Stage III breast cancer. *Breast Cancer Res Treat.* 2012; **132**(1): 51–9. [PubMed Abstract](#) | [Publisher Full Text](#)
113. Singh B, Berry JA, Shohar A, *et al.*: COX-2 overexpression increases motility and invasion of breast cancer cells. *Int J Oncol.* 2005; **26**(5): 1393–9. [PubMed Abstract](#) | [Publisher Full Text](#)
114. Simeone AM, Nieves-Alicea R, McMurtry VC, *et al.*: Cyclooxygenase-2 uses the protein kinase C/interleukin-8/urokinase-type plasminogen activator pathway to increase the invasiveness of breast cancer cells. *Int J Oncol.* 2007; **30**(4): 785–92. [PubMed Abstract](#) | [Publisher Full Text](#)
115. Costa C, Soares R, Reis-Filho JS, *et al.*: Cyclo-oxygenase 2 expression is associated with angiogenesis and lymph node metastasis in human breast cancer. *J Clin Pathol.* 2002; **55**(6): 429–434. [PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
116. Soslow RA, Dannenberg AJ, Rush D, *et al.*: COX-2 is expressed in human pulmonary, colonic, and mammary tumors. *Cancer.* 2000; **89**(12): 2637–2645. [PubMed Abstract](#) | [Publisher Full Text](#)
117. Wang ZM, Liu J, Liu HB, *et al.*: Abnormal COX2 protein expression may be correlated with poor prognosis in oral cancer: a meta-analysis. *Biomed Res Int.* 2014; **2014**: 364207. [PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
118. Spano JP, Chouahnia K, Morère JF, *et al.*: [Cyclooxygenase 2 inhibitors and lung carcinoma]. *Bull Cancer.* 2004; **91**(Suppl 2): S109–12. [PubMed Abstract](#)
119. Konturek PC, Nikiforuk A, Kania J, *et al.*: Activation of NFkappaB represents the central event in the neoplastic progression associated with Barrett's esophagus: a possible link to the inflammation and overexpression of COX-2, PPARgamma and growth factors. *Dig Dis Sci.* 2004; **49**(7–8): 1075–83. [PubMed Abstract](#) | [Publisher Full Text](#)
120. Chen XR, Besson VC, Palmier B, *et al.*: Neurological recovery-promoting, anti-inflammatory, and anti-oxidative effects afforded by fenofibrate, a PPAR alpha agonist, in traumatic brain injury. *J Neurotrauma.* 2007; **24**(7): 1119–31. [PubMed Abstract](#) | [Publisher Full Text](#)
121. Chen YJ, Quilley J: Fenofibrate treatment of diabetic rats reduces nitrosative stress, renal cyclooxygenase-2 expression, and enhanced renal prostaglandin release. *J Pharmacol Exp Ther.* 2008; **324**(2): 658–63. [PubMed Abstract](#) | [Publisher Full Text](#)
122. Lee DL, Wilson JL, Duan R, *et al.*: Peroxisome Proliferator-Activated Receptor- α Activation Decreases Mean Arterial Pressure, Plasma Interleukin-6, and COX-2 While Increasing Renal CYP4A Expression in an Acute Model of DOCA-Salt Hypertension. *PPAR Res.* 2011; **2011**: 502631. [PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
123. Alvarez de Sotomayor M, Mingorance C, Andriantsitohaina R: Fenofibrate improves age-related endothelial dysfunction in rat resistance arteries. *Atherosclerosis.* 2007; **193**(1): 112–120. [PubMed Abstract](#) | [Publisher Full Text](#)
124. Ramanan S, Kooshki M, Zhao W, *et al.*: PPARalpha ligands inhibit radiation-induced microglial inflammatory responses by negatively regulating NF-kappaB and AP-1 pathways. *Free Radic Biol Med.* 2008; **45**(12): 1695–1704. [PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
125. Urbanska K, Pannizzo P, Grabacka M, *et al.*: Activation of PPARalpha inhibits IGF-I-mediated growth and survival responses in medulloblastoma cell lines. *Int J Cancer.* 2008; **123**(5): 1015–24. [PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
126. Drukala J, Urbanska K, Wilk A, *et al.*: ROS accumulation and IGF-IR inhibition contribute to fenofibrate/PPARalpha-mediated inhibition of glioma cell motility *in vitro*. *Mol Cancer.* 2010; **9**: 159. [PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
127. Trojan J, Cloix JF, Ardourel MY, *et al.*: Insulin-like growth factor type I biology and targeting in malignant gliomas. *Neuroscience.* 2007; **145**(3): 795–811. [PubMed Abstract](#) | [Publisher Full Text](#)
128. D'Ambrosio C, Ferber A, Resnicoff M, *et al.*: A soluble insulin-like growth factor I receptor that induces apoptosis of tumor cells *in vivo* and inhibits tumorigenesis. *Cancer Res.* 1996; **56**(17): 4013–4020. [PubMed Abstract](#)

129. Toda K, Okada T, Miyaura C, *et al.*: **Fenofibrate, a ligand for PPARalpha, inhibits aromatase cytochrome P₄₅₀ expression in the ovary of mouse.** *J Lipid Res.* 2003; **44**(2): 265–270.
[PubMed Abstract](#) | [Publisher Full Text](#)
130. Zhao H, Zhu C, Qin C, *et al.*: **Fenofibrate down-regulates the expressions of androgen receptor (AR) and AR target genes and induces oxidative stress in the prostate cancer cell line LNCaP.** *Biochem Biophys Res Commun.* 2013; **432**(2): 320–5.
[PubMed Abstract](#) | [Publisher Full Text](#)
131. Liu X, Jang SS, An Z, *et al.*: **Fenofibrate decreases radiation sensitivity via peroxisome proliferator-activated receptor α -mediated superoxide dismutase induction in HeLa cells.** *Radiat Oncol J.* 2012; **30**(2): 88–95.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
132. Ge Y, Liu J, Yang X, *et al.*: **Fenofibrate enhances radiosensitivity of esophageal squamous cell carcinoma by suppressing hypoxia-inducible factor-1 α expression.** *Tumour Biol.* 2014; **35**(11): 10765–10771.
[PubMed Abstract](#) | [Publisher Full Text](#)
133. Liu J, Ge YY, Zhu HC, *et al.*: **Fenofibrate increases radiosensitivity in head and neck squamous cell carcinoma via inducing G2/M arrest and apoptosis.** *Asian Pac J Cancer Prev.* 2014; **15**(16): 6649–6655.
[PubMed Abstract](#) | [Publisher Full Text](#)
134. Collet P, Domenjoud L, Devignes MD, *et al.*: **The human semaphorin 6B gene is down regulated by PPARs.** *Genomics.* 2004; **83**(6): 1141–50.
[PubMed Abstract](#) | [Publisher Full Text](#)
135. Murad H, Collet P, Huin-Schohn C, *et al.*: **Effects of PPAR and RXR ligands in semaphorin 6B gene expression of human MCF-7 breast cancer cells.** *Int J Oncol.* 2006; **28**(4): 977–84.
[PubMed Abstract](#) | [Publisher Full Text](#)
136. Ge C, Li Q, Wang L, *et al.*: **The role of axon guidance factor semaphorin 6B in the invasion and metastasis of gastric cancer.** *J Int Med Res.* 2013; **41**(2): 284–92.
[PubMed Abstract](#) | [Publisher Full Text](#)
137. Correa RG, Sasahara RM, Bengtson MH, *et al.*: **Human semaphorin 6B [(HSA)SEMA6B], a novel human class 6 semaphorin gene: alternative splicing and all-trans-retinoic acid-dependent downregulation in glioblastoma cell lines.** *Genomics.* 2001; **73**(3): 343–8.
[PubMed Abstract](#) | [Publisher Full Text](#)
138. Murakami H, Murakami R, Kambe F, *et al.*: **Fenofibrate activates AMPK and increases eNOS phosphorylation in HUVEC.** *Biochem Biophys Res Commun.* 2006; **341**(4): 973–978.
[PubMed Abstract](#) | [Publisher Full Text](#)
139. Jiying W, Tao W, Jinrong Z, *et al.*: **Effect of combined arsenic trioxide and fenofibrate on epithelial-interstitial transformation and E-cadherin/snail transformation factor in human pulmonary carcinoma A549 cells.** *Journal of Third Military University.* 2012–14.
[Reference Source](#)
140. Tanaka T, Kohno H, Yoshitani S, *et al.*: **Ligands for peroxisome proliferator-activated receptors alpha and gamma inhibit chemically induced colitis and formation of aberrant crypt foci in rats.** *Cancer Res.* 2001; **61**(6): 2424–2428.
[PubMed Abstract](#)
141. Murtola TJ, Tammela TL, Lahtela J, *et al.*: **Cholesterol-lowering drugs and prostate cancer risk: a population-based case-control study.** *Cancer Epidemiol Biomarkers Prev.* 2007; **16**(11): 2226–32.
[PubMed Abstract](#) | [Publisher Full Text](#)
142. Rao A, D'Amico S, Balasubramanyam A, *et al.*: **Fenofibrate is effective in treating hypertriglyceridemia associated with HIV lipodystrophy.** *Am J Med Sci.* 2004; **327**(6): 315–8.
[PubMed Abstract](#) | [Publisher Full Text](#)
143. Koltai T: **Nelfinavir and other protease inhibitors in cancer: mechanisms involved in anticancer activity.** *F1000Res.* 2015; **4**: 9.
[Publisher Full Text](#)
144. Bonnet E, Ruidavets JB, Tuche J, *et al.*: **Apoptotic c-III and E-containing lipoparticles are markedly increased in HIV-infected patients treated with protease inhibitors: association with the development of lipodystrophy.** *J Clin Endocrinol Metab.* 2001; **86**(1): 296–302.
[PubMed Abstract](#) | [Publisher Full Text](#)
145. Samson SL, Pownall HJ, Scott LW, *et al.*: **Heart positive: design of a randomized controlled clinical trial of intensive lifestyle intervention, niacin and fenofibrate for HIV lipodystrophy/dyslipidemia.** *Contemp Clin Trials.* 2006; **27**(6): 518–30.
[PubMed Abstract](#) | [Publisher Full Text](#)
146. Thomas JC, Lopes-Virella MF, Del Bene VE, *et al.*: **Use of fenofibrate in the management of protease inhibitor-associated lipid abnormalities.** *Pharmacotherapy.* 2000; **20**(6): 727–734.
[PubMed Abstract](#) | [Publisher Full Text](#)
147. Collett GP, Betts AM, Johnson MI, *et al.*: **Peroxisome proliferator-activated receptor alpha is an androgen-responsive gene in human prostate and is highly expressed in prostatic adenocarcinoma.** *Clin Cancer Res.* 2000; **6**(8): 3241–8.
[PubMed Abstract](#)
148. Fauconnet S, Lascombe I, Chabannes E, *et al.*: **Differential regulation of vascular endothelial growth factor expression by peroxisome proliferator-activated receptors in bladder cancer cells.** *J Biol Chem.* 2002; **277**(26): 23534–43.
[PubMed Abstract](#) | [Publisher Full Text](#)
149. Suchanek KM, May FJ, Robinson JA, *et al.*: **Peroxisome proliferator-activated receptor alpha in the human breast cancer cell lines MCF-7 and MDA-MB-231.** *Mol Carcinog.* 2002; **34**(4): 165–171.
[PubMed Abstract](#) | [Publisher Full Text](#)
150. Jackson L, Wahli W, Michalik L, *et al.*: **Potential role for peroxisome proliferator activated receptor (PPAR) in preventing colon cancer.** *Gut.* 2003; **52**(9): 1317–1322.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
151. Li MY, Yuan H, Ma LT, *et al.*: **Roles of peroxisome proliferator-activated receptor-alpha and -gamma in the development of non-small cell lung cancer.** *Am J Respir Cell Mol Biol.* 2010; **43**(6): 674–83.
[PubMed Abstract](#) | [Publisher Full Text](#)
152. Palmer CN, Hsu MH, Griffin KJ, *et al.*: **Peroxisome proliferator activated receptor-alpha expression in human liver.** *Mol Pharmacol.* 1998; **53**(1): 14–22.
[PubMed Abstract](#)
153. Roberts RA, James NH, Hasmall SC, *et al.*: **Apoptosis and proliferation in nongenotoxic carcinogenesis: species differences and role of PPARalpha.** *Toxicol Lett.* 2000; **112**–113: 49–57.
[PubMed Abstract](#) | [Publisher Full Text](#)
154. Vanden Heuvel JP, Kreder D, Belda B, *et al.*: **Comprehensive analysis of gene expression in rat and human hepatoma cells exposed to the peroxisome proliferator WY14,643.** *Toxicol Appl Pharmacol.* 2003; **188**(3): 185–98.
[PubMed Abstract](#) | [Publisher Full Text](#)
155. Rao MS, Reddy JK: **Peroxisome proliferation and hepatocarcinogenesis.** *Carcinogenesis.* 1987; **8**(5): 631–636.
[PubMed Abstract](#) | [Publisher Full Text](#)
156. Wilk A, Urbanska K, Grabacka M, *et al.*: **Fenofibrate-induced nuclear translocation of FoxO3A triggers Bim-mediated apoptosis in glioblastoma cells in vitro.** *Cell Cycle.* 2012; **11**(14): 2660–2671.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
157. Wilk A, Wyczzechowska D, Zapata A, *et al.*: **Molecular mechanisms of fenofibrate-induced metabolic catastrophe and glioblastoma cell death.** *Mol Cell Biol.* 2015; **35**(1): 182–198.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
158. Han DF, Zhang J, Wei W, *et al.*: **Fenofibrate induces G₀/G₁ phase arrest by modulating the PPAR α /FoxO1/p27^{kip1} pathway in human glioblastoma cells.** *Tumor Biol.* 2015.
[PubMed Abstract](#) | [Publisher Full Text](#)
159. Tsao SC, Tsai MH, Chiu CF, *et al.*: **AMPK-dependent signaling modulates the suppression of invasion and migration by fenofibrate in CAL 27 oral cancer cells through NF- κ B pathway.** *Environ Toxicol.* 2014.
[PubMed Abstract](#) | [Publisher Full Text](#)
160. Grau R, Punzón C, Fresno M, *et al.*: **Peroxisome-proliferator-activated receptor alpha agonists inhibit cyclo-oxygenase 2 and vascular endothelial growth factor transcriptional activation in human colorectal carcinoma cells via inhibition of activator protein-1.** *Biochem J.* 2006; **395**(1): 81–88.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
161. Vamecq J, Colet JM, Vanden Eynde JJ, *et al.*: **PPARs: interference with Warburg's Effect and Clinical Anticancer Trials.** *PPAR Res.* 2012; **2012**: 304760.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
162. Sekiya M, Yahagi N, Matsuzaka T, *et al.*: **Polyunsaturated fatty acids ameliorate hepatic steatosis in obese mice by SREBP-1 suppression.** *Hepatology.* 2003; **38**(6): 1529–1539.
[PubMed Abstract](#) | [Publisher Full Text](#)
163. Kim HJ, Takahashi M, Ezaki O: **Fish oil feeding decreases mature sterol regulatory element-binding protein 1 (SREBP-1) by down-regulation of SREBP-1c mRNA in mouse liver. A possible mechanism for down-regulation of lipogenic enzyme mRNAs.** *J Biol Chem.* 1999; **274**(36): 25892–25898.
[PubMed Abstract](#) | [Publisher Full Text](#)
164. Guo K, Wang PR, Milot DP, *et al.*: **Regulation of lipid metabolism and gene expression by fenofibrate in hamsters.** *Biochim Biophys Acta.* 2001; **1533**(3): 220–232.
[PubMed Abstract](#) | [Publisher Full Text](#)
165. König B, Koch A, Spielmann J, *et al.*: **Activation of PPARalpha lowers synthesis and concentration of cholesterol by reduction of nuclear SREBP-2.** *Biochem Pharmacol.* 2007; **73**(4): 574–585.
[PubMed Abstract](#) | [Publisher Full Text](#)
166. Gamberdinger M, Clement AB, Behl C: **Cholesterol-like effects of selective cyclooxygenase inhibitors and fibrates on cellular membranes and amyloid-beta production.** *Mol Pharmacol.* 2007; **72**(1): 141–51.
[PubMed Abstract](#) | [Publisher Full Text](#)
167. Li Y, Ge M, Ciani L, *et al.*: **Enrichment of endoplasmic reticulum with cholesterol inhibits sarcoplasmic-endoplasmic reticulum calcium ATPase-2b activity in parallel with increased order of membrane lipids: implications for depletion of endoplasmic reticulum calcium stores and apoptosis in cholesterol-loaded macrophages.** *J Biol Chem.* 2004; **279**(35): 37030–9.
[PubMed Abstract](#) | [Publisher Full Text](#)
168. Youssef J, Badr M: **Extraperoxisomal targets of peroxisome proliferators: mitochondrial, microsomal, and cytosolic effects. Implications for health and disease.** *Crit Rev Toxicol.* 1998; **28**(1): 1–33.
[PubMed Abstract](#) | [Publisher Full Text](#)

169. Zungu M, Felix R, Essop MF: **Wy-14,643 and fenofibrate inhibit mitochondrial respiration in isolated rat cardiac mitochondria.** *Mitochondrion*. 2006; **6**(6): 315–22.
[PubMed Abstract](#) | [Publisher Full Text](#)
170. Yao CX, Li WY, Zhang SF, *et al.*: **Effects of Doxorubicin and Fenofibrate on the activities of NADH oxidase and citrate synthase in mice.** *Basic Clin Pharmacol Toxicol*. 2011; **109**(6): 452–6.
[PubMed Abstract](#) | [Publisher Full Text](#)
171. Scatena R, Martorana GE, Bottoni P, *et al.*: **Mitochondrial dysfunction by synthetic ligands of peroxisome proliferator activated receptors (PPARs).** *IUBMB Life*. 2004; **56**(8): 477–82.
[PubMed Abstract](#) | [Publisher Full Text](#)
172. Scatena R, Bottoni P, Martorana GE, *et al.*: **Mitochondrial respiratory chain dysfunction, a non-receptor-mediated effect of synthetic PPAR-ligands: biochemical and pharmacological implications.** *Biochem Biophys Res Commun*. 2004; **319**(3): 967–73.
[PubMed Abstract](#) | [Publisher Full Text](#)
173. Scatena R, Bottoni P, Vincenzoni F, *et al.*: **Bezafibrate induces a mitochondrial derangement in human cell lines: a PPAR-independent mechanism for a peroxisome proliferator.** *Chem Res Toxicol*. 2003; **16**(11): 1440–1447.
[PubMed Abstract](#) | [Publisher Full Text](#)
174. Grabacka M, Waligorski P, Zapata A, *et al.*: **Fenofibrate subcellular distribution as a rationale for the intracranial delivery through biodegradable carrier.** *J Physiol Pharmacol*. 2015; **66**(2): 233–247.
[PubMed Abstract](#)
175. Kukar T, Murphy MP, Eriksen JL, *et al.*: **Diverse compounds mimic Alzheimer disease-causing mutations by augmenting Abeta42 production.** *Nat Med*. 2005; **11**(5): 545–550.
[PubMed Abstract](#) | [Publisher Full Text](#)

Open Peer Review

Current Peer Review Status:

Version 2

Reviewer Report 28 September 2015

<https://doi.org/10.5256/f1000research.7072.r10247>

© 2015 Reiss K. This is an open access peer review report distributed under the terms of the [Creative Commons Attribution License](#), which permits unrestricted use, distribution, and reproduction in any medium, provided the original work is properly cited.

Krzysztof Reiss

Stanley S Scott Cancer Center, Louisiana State University Health Sciences Center, New Orleans, LA, USA

The authors responded to all my comments and suggestions. In my opinion, the revised version of this comprehensive review about anticancer effects of fenofibrate is acceptable for an Approved in F1000Research.

Competing Interests: No competing interests were disclosed.

I confirm that I have read this submission and believe that I have an appropriate level of expertise to confirm that it is of an acceptable scientific standard.

Reviewer Report 14 September 2015

<https://doi.org/10.5256/f1000research.7072.r10288>

© 2015 Czyz J. This is an open access peer review report distributed under the terms of the [Creative Commons Attribution License](#), which permits unrestricted use, distribution, and reproduction in any medium, provided the original work is properly cited.

Jarosław Czyz

Department of Cell Biology, Jagiellonian University, Krakow, Poland

This article provides a comprehensive and comprehensible summary of the research on potential anti-cancer activities of fenofibrate. The author thoroughly describes the available data on the possible mechanisms of fenofibrate effect on cancer cells, however he could have concentrated more on the compilation of these data to emphasize their scientific merit. For example, I would suggest an addition of a more in-depth conclusive summary of the direct/indirect effects of fenofibrate on cancer cells/normal (stromal) cells in vivo/in vitro. Moreover, due to the systemic

tolerability of fenofibrate, a possibility of its application in palliative treatment/metastasis prevention of advanced cancers could be more thoroughly discussed. Please, also note that the reference 82 should be moved to Table 8, because it shows the augmentation of cell adhesion rather than the "anti-adhesion" effects. Reference 82 on page 11 and 13 contains a mistake in the name of the first author.

Competing Interests: No competing interests were disclosed.

I confirm that I have read this submission and believe that I have an appropriate level of expertise to confirm that it is of an acceptable scientific standard, however I have significant reservations, as outlined above.

Author Response 28 Sep 2015

Tomas Koltai, Centro de Diagnostico y Tratamiento de la Obra Social del Personal de la Alimentación, Buenos Aires, Argentina

Dear Dr. Czyz

Thank you for your review.

Author (reference 82) mentioned on pages 11 and 13 has an error. It says Piwowarczyc K and should say **Piwowarczyk** K. This error will be corrected.

Table 7 will be renamed to: **FF activity on cell adhesion and chemokines**. In this way, the same table will harbour pro and anti adhesion activities.

We did not discuss in depth clinical achievements with FF in cancer, because we tried to avoid any speculative idea or considerations not based on hard evidence. We used FF in patients with metastatic clear cell renal carcinoma and observed better response to sunitib and to everolimus. In cases of resistance to a second series of sunitib indicated for relapsed tumor, FF re-sensitized patients to sunitib. We also found that patients with metastatic RCC receiving FF showed a longer progression free survival than patients without FF. We did not find a preventive effect against metastasis in the clinical setting. These data were not published because the number of patients was too small and the follow up period was too short, so we decided to postpone any publication until we could gather enough evidence to give adequate support to FF as part of the treatment of renal cell carcinoma (RCC).

We will produce a third version, correcting the issues you remarked.

Sincerely yours

Competing Interests: No competing interests

Version 1

Reviewer Report 11 May 2015

<https://doi.org/10.5256/f1000research.6595.r8393>

© 2015 Reiss K. This is an open access peer review report distributed under the terms of the [Creative Commons Attribution License](#), which permits unrestricted use, distribution, and reproduction in any medium, provided the original work is properly cited.

Krzysztof Reiss

Stanley S Scott Cancer Center, Louisiana State University Health Sciences Center, New Orleans, LA, USA

This is an excellent comprehensive review of the literature related to Fenofibrate anticancer effects, which definitely deserves to be indexed after revision.

I have three comments which should be implemented:

1. It should be mentioned that fenofibrate is a prodrug, which is processed by blood esterases to fenofibric acid, and that fenofibric acid is potent agonist of PPARα. Therefore, there are two very different substances, fenofibrate and fenofibric acid, which could have very different anticancer properties. As far as I understand the system, mitochondrial and growth factor-mediated effects are rather associated with unprocessed fenofibrate, which in opposite to fenofibric acid is capable of interacting with biological membranes.
2. Reference 89 in table 6 should be updated (see below); and the issue of Fenofibrate and mitochondrial respiration deserves a separate paragraph since it explains how unprocessed fenofibrate can target tumor cells, being at the same time much less harmful to normal cells. Other described mechanisms could be involved as a consequence of this primary mitochondrial action, which actually happens in minutes.

Wilk A, Wyczechowska D, Zapata A, Dean M, Mullinax J, Marrero L, Parsons C, Peruzzi F, Culicchia F, Ochoa A, Grabacka M, Reiss K. [Molecular mechanisms of fenofibrate-induced metabolic catastrophe and glioblastoma cell death](#). Mol Cell Biol. 2015 Jan;35(1):182-98. doi: 10.1128/MCB.00562-14. Epub 2014 Oct 20. PubMed PMID: 25332241; PubMed Central PMCID: PMC4295376.

3. Reference 158 has a mistake it should be MCB 2015 instead of MCB 2005

Competing Interests: No competing interests were disclosed.

I confirm that I have read this submission and believe that I have an appropriate level of expertise to confirm that it is of an acceptable scientific standard, however I have significant reservations, as outlined above.

Author Response 13 May 2015

Tomas Koltai, Centro de Diagnostico y Tratamiento de la Obra Social del Personal de la Alimentación, Buenos Aires, Argentina

Dear Dr. Krzysztof Reiss

Thank you for your kind contribution to this review.

A new version is under way, which will include all the issues you remarked:

1. A figure will be introduced which will show the molecular structure of FF and fibrin acid. The difference between the pharmacologic actions of both will be discussed.
2. Membrane rigidity due to FF will be explained under a new heading and the importance of this effect will be further discussed. The difference in cell distribution of FA and FF will be also considered.
3. Reference in Table 6 will be updated and reference 158 will be corrected.

Remains sincerely yours

Tomas Koltai

Competing Interests: There are no conflicts of interests

The benefits of publishing with F1000Research:

- Your article is published within days, with no editorial bias
- You can publish traditional articles, null/negative results, case reports, data notes and more
- The peer review process is transparent and collaborative
- Your article is indexed in PubMed after passing peer review
- Dedicated customer support at every stage

For pre-submission enquiries, contact research@f1000.com

F1000Research