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REVIEW

Thymoquinone and Pyruvate Metabolism in Cancer-Associated Fibroblasts: Emerging Therapeutic Insights

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Abstract

Overview: Cancer continues to be a major global health burden, with GLOBOCAN 2020 reporting 19.3 million new cases and 10 million deaths. Despite advances in treatment, aggressive cancers especially liver and pancreatic remain difficult to manage. Lifestyle factors such as smoking, alcohol use, obesity, and infections contribute significantly to the rising incidence. Conventional therapies often face limitations due to resistance and late-stage progression. Increasing research now focuses on metabolic vulnerabilities within the tumor microenvironment, particularly the role of cancer-associated fibroblasts (CAFs). Driven by signals like TGF-β, PDGF, and IL-6, CAFs fuel tumor growth through metabolic reprogramming and the Reverse Warburg effect. Pyruvate, a central metabolite in glycolysis, plays a key role in these energy-driven processes. **Methods:** A structured search of PubMed and Google Scholar was performed using the keywords cancer, pyruvate pathways, Thymoquinone, Nigella sativa, and cancer-associated fibroblasts. Studies addressing TQ's anticancer and metabolic effects were reviewed. **Results:** Thymoquinone (TQ), the main bioactive constituent of Nigella sativa, possesses antioxidant, anti-inflammatory, and antiproliferative actions. Evidence shows that TQ can influence glycolysis, mitochondrial activity, lactate production, and redox balance. However, studies specifically exploring its effects on pyruvate metabolism in CAFs remain limited. Early observations suggest that TQ may interfere with CAF-mediated metabolic support to tumors. **Conclusion:** This review highlights the potential of TQ in targeting cancer metabolism, particularly pyruvate-related pathways in cancer cells and CAFs. Further focused research may help translate these insights into effective metabolic-based therapeutic strategies.

Keywords: Thymoquinone- Pyruvate pathways- Human- Health- Cancer- Health risk

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Introduction

The cancer pathology is still an unsolved mystery to mankind. The notorious feature of cancer lies in the insidious buildup of genetic mutations that disrupt normal physiological processes, increase free radical production, and alter essential cell signaling pathways [1]. These changes accumulate over decades and are often accelerated by modifiable lifestyle risk factors such as smoking, poor diet, and lack of exercise [2]. Several comorbid conditions such as diabetes, hypertension, and alcohol abuse, chronic stress, and hormonal imbalances can also contribute directly or indirectly to cancer development. Collectively, these risk factors play a significant role in the slow progression of carcinogenesis. Owing to its natural course of progress over years, cancer tends to occur more frequently in older populations [3]. In most of the underdeveloped and developing countries, awareness and early detection of cancer are lacking, and nearly 80% of the patients are diagnosed at advanced stages. Delayed diagnosis in terminal stages contributes to cancer-related deaths, with therapeutic interference proving no benefits

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[4]. As per GLOBOCAN (Global Cancer Observatory) 2020, the incidence of cancer globally was 19.3 million, with approximately 10.0 million cancer-related deaths in the same year. The most prevalent cancer is breast cancer, followed by lung, colorectal, prostate, and gastric cancer [5]. The mortality rate of lung cancer is greatest among others. It has been estimated that the global cancer burden will rise to 28.4 million cases in 2040. In 2025, approximately 2,041,910 new cancer cases are projected to be diagnosed in the United States, with an estimated 618,120 cancer-related deaths. The most frequently reported cancers are, in order of estimated incidence, breast, prostate, lung and bronchus, colorectal, melanoma of the skin, bladder, kidney and renal pelvis, non-Hodgkin lymphoma, uterine corpus, pancreatic, leukemia, thyroid, and liver and intrahepatic bile duct cancers [5, 6].

Cancer-associated Fibroblasts (CAFs) are a heterogeneous stromal population in the Tumor Microenvironment (TME) play a vital role on regulating the tumor initiation and its further progression [7]. Besides their structural and functional supports to tumors, CAFs also undergo a profound reprogramming that is peculiarly potentiated by pyruvate handling, enhanced glycolysis, and lactate production [8]. These metabolic coupling highly nurtures the cancer cells for attaining the energy requirement for tumor growth (Figure 1). Notably, these metabolic and phenotypic features of CAFs closely resemble fibroblast activation observed in several cancer-associated comorbidities, including diabetes, obesity, cardiovascular disease, and chronic inflammatory and fibrotic disorders. Shared drivers such as hypoxia, oxidative stress, inflammatory cytokines, and dysregulated energy metabolism promote fibroblast activation across these conditions, suggesting common mechanistic pathways [9]. Consequently, CAFs may serve as a biological bridge linking tumor metabolism with systemic metabolic and inflammatory comorbidities, highlighting the importance of targeting CAF metabolism not only for cancer therapy but also for broader disease modulation.

Cancer Associated Fibroblasts- A trump card for reprogramming

Fibroblasts are the stromal cells that help for maintaining the integrity of the extracellular matrix (ECM), wound healing and tissue repair. Normally, after execution of the proposed physiological processes, these fibroblasts rest in a quiescent phenotype, on requirement, they are being activated by different means of complex and controlled signaling mechanisms [10]. Tumor cells bypass normal regulatory signals, reprogramming fibroblasts into cancer-associated fibroblasts [11]. Tumor cells secrete excessive amount of Transforming Growth Factor – β (TGF-β), platelet- derived growth factor (PDGF), interleukin -6 (IL-6) and extracellular vesicles carrying microRNAs drive fibroblast activation and metabolic rewiring [12]. Further, chronic hypoxia and oxidative stress stabilize the CAFs phenotype and their characteristic activation of tumor supports [13]. CAFs, are highly heterogenous in nature (Table 1) and exhibit sustained expression of different biomarkers including α-SMA, FAP, and ECM-remodeling proteins [14]. The resulting CAFs promote angiogenesis, immunosuppression, and tumor invasion, making them as a critical stromal accomplice in cancer progression. Tumor activated CAFs attained a characteristic myofibroblastic phenotype that elevate the expression of α-smooth muscle actin (α-SMA), fibroblast activation protein (FAP), and increased secretion of pro-tumorigenic cytokines [15]. CAFs remodel the ECM extensively, creating a stiffened and desmoplastic niche that supports tumor growth, invasion, and metastasis. They also modulate angiogenesis, immune evasion, and therapeutic resistance through paracrine signaling involving TGF-β, IL-6, and other soluble mediators. Importantly, CAFs display remarkable heterogeneity, with distinct subpopulations exerting diverse and sometimes opposing functions ranging from tumor promotion to immunomodulation [16].

Although CAFs play a crucial role in promoting tumor growth and aiding immune evasion, their complete elimination has been shown to potentially increase metastatic spread rather than inhibition. Recent literature emphasizes that reprogramming rather than removing CAFs may offer a more effective strategy to enhance anti-tumor immune responses [20, 21, 25]. One promising

Table 1. Different Subtypes of CAFs and Their Drug Discovery Significance

Cancer Associated Fibroblast (CAFs) subtype	Markers	Signaling pathways	Importance in drug discovery	References
Myofibroblastic CAFs (myCAFs)	α-SMA, COL1A1, TAGLN, MYH11	TGF-β/SMAD	TGF-β inhibitors, LOX inhibitors, stromal modulators	[17,15]
Inflammatory CAFs (iCAFs)	IL-6, IL-1β, LIF, CXCL12, CCL2	NF-κB, JAK/STAT	Cytokine inhibitors (IL-6/STAT3 blockers, CXCR4 inhibitors)	[18]
Antigen-presenting CAFs (apCAFs)	MHC-II (HLA-DR, CD74, CIITA), no CD80/CD86	IFN-γ–induced MHC-II	Strategies to modulate CAF–T-cell interactions, combined checkpoint inhibitors	[19]
Vascular CAFs (vCAFs)	PDGFRβ, RGS5, NG2, DES	PDGF, VEGF	Anti-VEGF/PDGF therapies	[15,16, 20,21]
Metabolic CAFs (meCAFs)	MCT4, LDHA, glycolytic enzymes	HIF-1α, glycolysis	MCT4 inhibitors, glycolysis modulators	[22, 23]
Stem-like CAFs	FAP, PDPN, CD29, stemness markers	Wnt, Notch, TGF-β	Plasticity modulators, fibroblast reprogramming	[24]

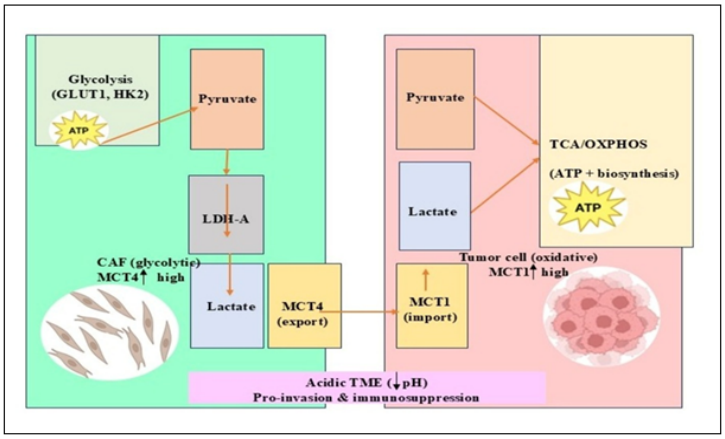

Figure 1. Cancer Associated Fibroblasts (CAFs) Help for Enhanced Proliferation of Cancer Cells by Providing the Lactate to Produce more Energy Currencies (ATPs)

approach involves the use of fibroblast-targeted lipid nanoparticle (LNP) delivery systems to downregulate key metabolic enzymes such as hexokinase 2 (HK2) and mitochondrial cytochrome c oxidase I (MTCO1) [26]. Suppressing myofibroblast differentiation from the fibroblast, reducing the deposition of the ECM and cytokine regulation are the important strategies for the CAFs reprogramming (Table 1). But, many of the bioactive compounds, including thymoquinone face various challenges such as poor solubility, adequate bioavailability, and impaired systemic distribution. To overcome, nanotechnology greatly serves as alternatives [23, 24, 25, 27]. This metabolic modulation induces the expression of major histocompatibility complex class II (MHC II) molecules and pro-inflammatory cytokines, thereby facilitating immune cell infiltration into the tumor microenvironment. Furthermore, this reprogramming strategy has been associated with reduced angiogenesis, polarization toward the pro-inflammatory M1 macrophage phenotype, and increased infiltration of lymphocytes, collectively contributing to a more robust anti-tumor immune landscape [28]. Targeting CAFs offers a promising strategy to complement existing immunotherapies and chemotherapies [17, 18, 19]. This approach aims to shift the tumor microenvironment (TME) from one that supports tumor growth to one that promotes anti-tumor immune responses [29].

As cancer is fundamentally a disease driven by genetic mutations, it disrupts numerous metabolic pathways one of the most critical being pyruvate metabolism [30]. Pyruvate is a key intermediate in several metabolic pathways and is produced from glucose during glycolysis. Usually in hypoxic conditions pyruvate is converted to lactate and NAD+ [31]. In cancer cells, instead of pyruvate being driven into the mitochondria for ATP production through the citric acid cycle it is preferentially converted into lactate [32]. In cancer cells there is an increase of lactate concentration [33]. Lactate is transported out into extracellular fluid by monocarboxylate transporters (Figure 1). This decreases pH surrounding cancer cells and helps in proliferation of cancer cells [34]. CAFs export lactate into the tumor microenvironment, which is subsequently taken up by cancer cells. Inside cancer cells, lactate is converted back into pyruvate and funneled into the citric acid cycle, thereby synthesizing large amounts of ATP. Cancer cells have high demand for ATP, which is fulfilled through cooperation with the surrounding CAFs [35].

The present review focuses on cancer associated fibroblasts effectively alter the pyruvate metabolism an important mediating pathway in malignant cells, hence, targeting CAFs and their associated pyruvate metabolism could be of prominent therapeutic targets for cancer therapy (Figure 2). But the studies are scarcely available on this aspect and the present study paying greater attention on bioactive compounds, particularly, on thymoquinone, that were shown to modulate the lactate metabolism of the cancer cells. We have searched and portrayed a comprehended report on the recent literature from 2015 to 2025 by using Google scholar, PubMed. In PubMed database we employed Boolean search by entering key words such as Nigella sativa, thymoquinone, pyruvate pathways, cancer, and cancer associate fibroblasts.

Mitochondrial pyruvate transporters as profound regulators in cancer proliferation

Mitochondria not only produce the cell' energy currencies, butt, also act as an important mediator for chemotherapeutics. Recent studies have highlighted the critical role of mitochondrial pyruvate carrier 1

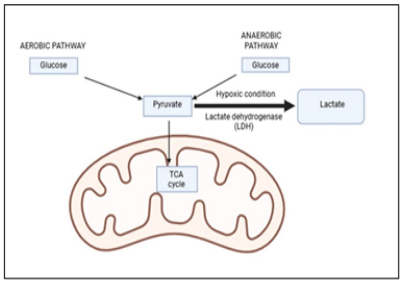

Figure 2. Pyruvate Metabolism in Mitochondria of the Cells. Pyruvate is synthesized under aerobic and anaerobic conditions. Pyruvate then enters into mitochondria for Tricarboxylic Acid cycle (TCA cycle) or otherwise known as citric acid cycle. In hypoxic conditions pyruvate in converted into lactate in the presence of LDH

Table 2. Different Isozymes of Pyruvate Kinase

Sl. No.	Subtype	Functions	Reference
1	Pyruvate kinase Liver (PKL)	Converting the phosphoenolpyruvate (PEP) into pyruvate at the final step of glycolysis. Liver specific isoform of pyruvate kinase (PKL), produced from the PKLR gene for maintaining overall energy homeostasis in the body.	[43]
2	Pyruvate kinase red blood cell (PKR)	Pyruvate kinase R (PKR), the isoform of the PKLR gene found in red blood cells, plays a vital role in maintaining erythrocyte energy production, structural integrity, and overall cell viability. PKR facilitates the transformation of phosphoenolpyruvate (PEP) into pyruvate, generating ATP from ADP in the process. Since mature red blood cells lack mitochondria, this glycolytic step supplies nearly half of their total ATP requirement.	[44]
3	Pyruvate kinase muscle1 (PKM1)	It exists in an active tetrameric form and consistently converts phosphoenolpyruvate (PEP) to pyruvate, supporting a high rate of glycolysis and efficient ATP generation crucial for energy-demanding tissues such as the brain, heart, and muscles.	[45]
4	Pyruvate kinase muscle 2 (PKM2)	Can exist as active tetramer or inactive dimer. Regulates aerobic glycolysis in cancer cells, enabling continued lactate production despite the presence of oxygen a hallmark of the Warburg effect. Converts Phosphoenol Pyruvate (PEP) into pyruvate in cancer cells.	[46]

(MPC1) in regulating cancer metabolism and genesis [36]. Nonetheless, the genetic mutations strongly affect the physiological functions, and the mutations on mitochondrial pyruvate carriers, pyruvate dehydrogenase, pyruvate carboxylase are merely enhancing the chances for the development of heart failure, neurodegeneration, and cancer [31]. On MPC1 and MPC2, the mitochondrial pyruvate carriers, those mutations impair the accompanied transportation, compelling the cells to rely more heavily on glycolysis for energy production [37]. Aggressiveness of several cancer types could be charecterized with their modulated their MPC1 expression over the normal counterparts, and making the prognosis in to challengeable ones. In hepatocellular carcinoma (HCC), MPC1 levels are significantly lower than normal. Increasing MPC1 expression under the regulation of the studies showed that the Peroxisome proliferator-activated receptor gamma coactivator-1 alpha (PGC1α) and Nuclear respiratory factor 1 (NRF1) are prominent therapeutic targets for modulating the MPC1 to slow tumor growth and improve the Effectiveness [38]. Further, sorafenib and doxorubicin had promoted apoptosis through elevated reactive oxygen species production [39]. Hence, the pyruvate regulators of the mitochondria become a promising cancer therapeutic target on recent scientific era.

Role of pyruvate kinase in cancer

The final stage of glycolysis, wherein one ATP is produced by converting phosphoenolpyruvate to pyruvate, is facilitated by the enzyme pyruvate kinase (PK). PK is one of the dynamic enzymes that determine the cell's metabolism, of it. Thus, the enzyme plays a pivotal role as oncogenic pathways that are essential for glycolysis in cancer cells [40]. Though, PK subtype, pyruvate kinase M2 (PKM2) is also significantly found within different tissues, embryonic tissue, testis, ovary, adrenal gland, pancreatic islet cells, thymus, nephron and leucocytes. The cancer cells prefer PKM2 since; it supports the anabolic metabolism favoring the cancer growth (Table 2). Further, the cancer cells over express PKM2 for maintaining the tumor morphogenesis and tumor microenvironment (TME) [41] (Figure 3). The cancer cells adopted different strategies to mainintaing high level of PKM2 by high expression of membrane proteins, including GLU1 than the other tissues. They also produce alternative isoforms of PKM2, because it provides metabolic, transcriptional, and phenotypic plasticity, which tumor cells exploit to survive, proliferate, and resist therapy [11-13] [42].

Cancer Associated Fibroblast and Pyruvate Metabolic regulation in Tumour Microenvironment (TME)

The Warburg effect frequently found on cancer growth because the cancer cells preferably down-regulate the oxidative phosphorylation and up regulation of glycolytic carbon flux. Thus, they can able to divert the pyruvate from the citric acid cycle for up regulating the PKM2, hypoxia-inducible factor (HIF-1) and for suppressing the tumor protein (p53) [47]. Together, with PKM2, the HIF-

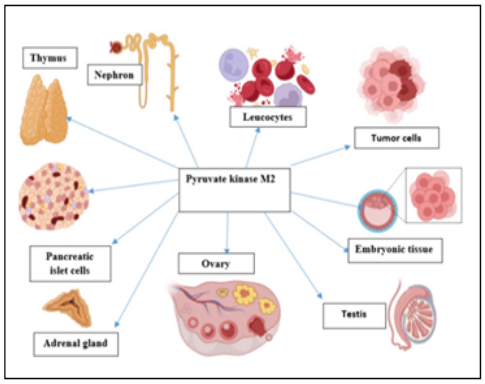

Figure 3. Role of Pyruvate Kinase M2 in Different Tissues

Table 3. Different Chemotherapeutic Targets on Cancer Associated Fibroblasts

Targets on Cancer Associated Fibroblast	Bioactive compounds	References
Cancer Associated Fibroblast activation	Resveratrol, curcumin	[62, 63]
Glycolysis	Dichloroacetate (DCA), lonidamine	[64]
Lactate transport	Syrosingopine	[65, 66]
Extra cellular Matrix remodeling	Nintedanib	[67]
Inflammation	Thymoquinone	[68]
Epigenetics	miR-34a	[69]

Table 4. Indirect Regulation of CAF Activity Through Key Signaling and Metabolic Pathways by Thymoquinone

Compound	Direct Evidence on CAFs	Indirect Evidence on CAF-Regulated Pathways	Key Pathways Modulated	Biological Relevance to CAF Activity	References
Thymoquinone	Scarcely available	Inhibited IL-6, NF-κB and lowered the expression of HIF-1α and MMP9	TGF-β, NF-κB, MMPs, IL-6/STAT3, HIF-1α,	Reduction of cytokine secretion, Activation of EMT pathways and inflammation under the CAF influence	[74]
	None	TGF-β/SMAD inhibition, ROS reduction, NF-κB and IL-6 down regulation	TGF-β, IL-6, NF-κB	Deactivation and or reprogramming of CAFs in TME	[75]
	None	Downregulates NF-κB, HIF-1α, PKM2, LDH-A; decreases lactate	NF-κB, HIF-1α, metabolic pathways (Warburg effect)	May interfere with CAF–cancer metabolic coupling	[74]
	Moderate	TGF-β1-induced fibroblast deactivation, down regulation of MMP expression	MMPs and TGF-β	Reprogramming of CAF for enhancing the anti-cancer activity	[76]

1 induces the cancer cell survival, cancer angiogenesis, glycolysis under hypoxic conditions [48]. Further, this HIF-1 up regulates transcription of Monocarboxylate Transporter 1 (MCT1), Lactate Dehydrogenase A (LDHA) and make functionally inactive Pyruvate Dehydrogenase Kinase 1 (PDK1) at cellular level for preventing the mitochondrial pyruvate oxidation [45, 46, 49]. This pro-glycolytic, pro-tumor arm (HIF-1α / PKM2 axis) is counteracted by the wild type p53 through, two important transcriptional factors, i.e., Mir-34a and TIGAR (tp53 induced glycolysis and apoptosis regulator) that implement the metabolic normal check points on pyruvate metabolism and inhibit the tumor progression [50]. But, p53 is mostly silenced and or inactivated in cancer cells. In the presence of dimeric PKM2, the mutated/ suppressed p53 unable to impair the pyruvate production, decreases oxidative phosphorylation [46]. In further, it could not inhibit the accumulation of glycolytic intermediates at cellular level through the pentose phosphate pathway (PPP). This accumulation eventually helps synthesis and further proliferation of cancer cells [51].

In the Reverse Warburg effect, CAFs rather than the tumor cell themselves shift their metabolism towards aerobic glycolysis [51]. Under the influence of tumor-derived signals, these cancer friendly fibroblasts enhance their glycolytic activity and release substantial amounts of metabolites such as pyruvate and lactate into the tumor microenvironment [52]. The cancer cells later absorb these energy-rich compounds and channel them into their mitochondria and export to tricarboxylic acid (TCA) cycle and oxidative phosphorylation [53]. The CAFs helps enabling them to fulfill the increased energy requirement. Visualizing the significance of pyruvate produced by CAFs in tumor metabolism has paved the way for innovative therapeutic strategies [43, 44, 54]. Hence, the CAFs are more promising candidates for therapeutical discovery on cancer research. Targeting the MCTs could be one of the perspective candidates to aim the shunting of CAFs influenced lactate signaling on TME [55].

Various bioactive compounds were shown to have targeted the CAFs by deactivating, modulating and or reprograming their signals for favoring chemotherapeutic achievements [56, 57, 58]. Several key targets are identified by the intensive research programs. Consequently, a range of bioactive compounds has been explored to inhibit CAF function, disrupt CAF–cancer metabolic symbiosis, and restore anti-tumor immune responses (Table 3). Deoxyglucose (2-DG) and 3-bromopyruvate are one among them that inhibit glycolytic enzymes and hence decrease aerobic glycolysis (Warburg effect) [59, 60]. These compounds were shown to inhibit metabolic activation, to disturb the inflammatory pathways by preventing the cancer dependent symbiosis and paracrine mechanisms [61]. These agents inhibit the tumor progression and tumor- immune responses.

Dichloroacetate (DCA) inhibits pyruvate dehydrogenase kinase (PDK) and allows the conversion of acetyl CoA in to TCA cycle [64]. Further, Warburg effects increase the lactate concentrations and the cancer cells pumped out them for decreasing the pH around them. CAFs were shown to activate the monocarboxylate transporters on this acidified milleu [62, 63]. This dropped pH level also reduces the activity of immune systems especially, the cytotoxic T cells [70]. Further, these activate matrix metalloproteinases / MMPs that helps for metastasis. Additively lactic acid formed around the cells activates metalloproteinases that acts on proteins favoring metastasis. Once the accumulated lactate is surplus, its

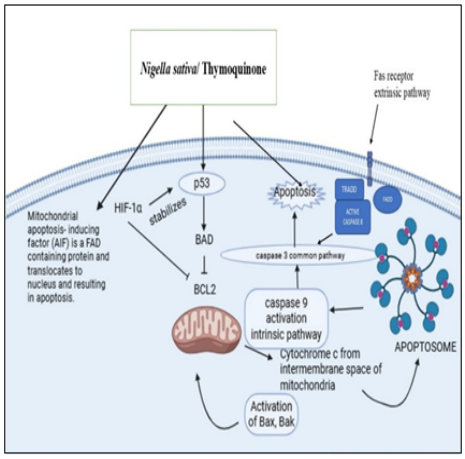

Figure. 4 The Extract of Nigella Sativa on Apoptotic Pathways. Proposed apoptotic pathways thymoquinone (TQ). Reduction in ROS helps in prevention of cancer formation. Reduction of NF-kB, IL-8, XIAP, Bcl2 and increase of Bax, caspase 3,8 and p53 finally contributes to apoptotic induction and that resulting cancer cell death [78].

further converted back to pyruvate which gets diverted into citric acid cycle and further into oxidative phosphorylation provided there is enough oxygen availability, culminating as an energy source for cancer cells [71].

Hexokinase enzyme, one among them and is used to convert the glucose into glucose-6-phosphate, the step that determines the rate of glycolysis, is one of the over-expressed genes among the cancer cells, particularly, hexokinase II. The studies showed that cancers could alter the P13K-AKT pathway, for modulating the increased HK II (HK2) expression as reported in osteosarcoma, CAFs regulate the HIF-1α in tumor milieu besides the tumors, and it was shown that HIF-1α could elevate hypoxia response elements (HREs) [72]. Though, direct evidences, are scarcely available, TQ was shown to inhibit most of the pathways that interrelate the tumor and CAFs coordination [68]. While some tumor cells favor the glycolytic route, others opt for oxidative phosphorylation as their energy source [23, 73].

Several studies showed that TQ have shown to inhibit different members of major pathways influenced by the CAF for favoring the tumor growth such as GF-β (CAFs), IL-6/NF-κB (iCAFs), and metabolic pathways (meCAFs) [22, 23]. Despite of direct analysis, these results correlated with the hypothesis that TQ could inhibit the several signaling pathways related to CAF induced tumor activation. Hence, there is a huge research gap in fulfilling the molecular characterization of the individual CAF subtypes under TQ influences [15]. The effects of the TQ under CAF modulation could have been tabulated in the present study as constructed from selected publication (Table 3 and 4).

TQ inhibited HK2 through the P13/AKT signaling on colorectal and breast cancer [23]. In HCT116 and SW480 CRC cells, TQ was shown to inhibit the invasiveness and migration through the inhibition of HK2. Further, the study showed that TQ modulated the EMT pathways by HK2 inhibition. Further, TQ was shown to induce and activate the sensitivity of natural killer cells (NK cells) against human prostate cancer cells (PC3-RFP cells). The study further showed that TQ inhibited NF-κB by suppressing the PI3/AKT through the upregulation of PTEN and Nrf2 antioxidant pathway. TQ also was shown to activate the macrophage and antitumor cytokines on Jurkat T cell line co- culture [23, 68]. Nigella sativa is one of the medicinal plants that exerts multiple bioactive nature against different cancer cells (Figure 4). TQ is well known for their role in regulation of apoptosis, especially in cancer (Figure 4). Studies showed that TQ acts as a promising adjuvant when combined along with chemotherapeutic drugs. It has been noticed that TQ acts on various cancer cell lines with a synergistic effect and enhanced the efficacy of conventional chemotherapeutic agents by acting through apoptotic pathways [77].

Further, TQ induces autophagy, decreased ERK ½, MMP 2, 9 and TWIST 1. TQ Inhibits JAK/STAT, MAPK and PI3K/Akt/ mTOR signaling pathways. Nuclear factor kappa B (NF-κB), Interleukin-8 (IL-8), X-linked inhibitor of apoptosis protein (XIAP), B-cell lymphoma 2 (Bcl 2), BCL2 associated X, apoptosis regulator (Bax), tumor protein p53 (p53), Reactive oxygen species (ROS), Extracellular Signal-Regulated Kinase (ERK), Matrix Metalloproteinase (MMP), Signal Transducer and Activator of Transcription (STAT), Mitogen-Activated Protein Kinase (MAPK), Phosphoinositide 3-kinase/ Protein Kinase B pathway (PI3K/Akt) [74, 78]. Hence, TQ could increase and decrease the apoptotic induction through the ROS regulation on cancer sites (Figure.5). Interestingly, TQ was shown to upregulate the apoptosis through the disrupting the glucose metabolism [23]. The TQ, a kind of monoterpene derivatives, plays an important role on the glucose metabolism of the cancer cells while simultaneously regulating the apoptosis induction (Table 5). Meanwhile, TQ enhance the ROS at sub- lethal level, acted dependent on the concentration, cellular redox capacity and exposure.

Many of the TQ related compounds, such as Thymol, monoterpene derivative was found to kill bladder cancer cells by inducing apoptosis through intrinsic pathway by

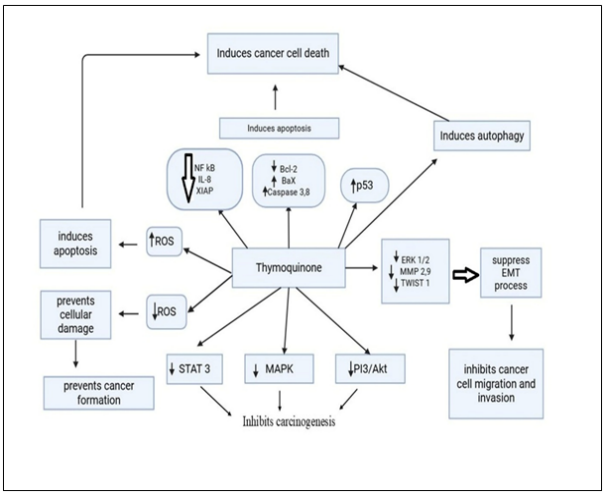

Figure 5. Thymoquinone Acts as Double- side Sword on Apoptosis Pathways. The thymoquinone may increase and decrease ROS level by metabolic activation according to the physiological requirements

Table 5. Thymoquinone Play Dynamic Pivotal Role in Glucose Metabolic Pathways Based on Cancer Types

Sl. No.	In vitro/ in vivo models	Objective of the study	Study design	Major outcomes	Reference
1.	CRC (Colorectal cancer) cells	Effect of TQ in modulating PI3K-AKT/HK2- mediated deregulation in colorectal cancer (CRC) cells	TQ Induced Cell Death in CRC Cells, Cytotoxicity (MTT) and Cell Doubling Assays	TQ Inhibited Hexokinase 2 via Modulating the PI3K-AKT Pathway. TQ action on CRC cells, showed its potential to be used as an antimetabolite drug, but further study on animal models is needed for elucidating the moolecular mechanisms.	[23]
2.	HEK 293	To investigate the potential anti-cancer effects of TQ through its targeted inhibition of hypoxia-inducible factor-1 alpha (HIF-1α).	Luciferase assay on a library of 502 natural compounds in HEK293 cells, HRE and VEGF luciferase activity in Caki-1 renal cancer cells, In Hypoxic Renal Cancer Cells	TQ acted as a novel inhibitor of HIF-1α, resulting in the downregulation of key anaerobic glycolysis-related genes such as CA-IX, PDK1, GLUT1, and LDHA. It reduced HIF-1α transcriptional activity and increased extracellular lactate levels.	[74]
3.	Colorectal cancer, HCT 116	Anti-proliferative effect and metabolic activity of TQ (TQ) on colon cancer cells (HCT-116).	Cell viability was determined by MTT analysis, Glucose and lactate concentrations were measured from cell culture supernatants for RPMI medium	Antiproliferative action in 40-200 µM concentrations, Glucose level of supernatant was 412±19.7 mg/dL TQ group, Lactate level was 8±1.1 µM in TQ group. TQ had an antiproliferative effect on HCT-116 and inhibitory effect on a glycolytic pathway.	[79]
4.	INS-1 832/13 cells	TQ normalizes insulin secretion from pancreatic β-cells under glucose overload via regulation of malonyl-CoA	INS-1 832/13 cell and pancreatic islet preparation and culture, Glucose-stimulated insulin secretion (GSIS)	TQ regulated NAD(P)H/NAD(P)+ ratios via a quinone-dependent redox cycling mechanism. TQ enhanced the sensitivity of β-cell metabolic pathways to glucose and GSIS under normal conditions as well as under hyperglycemia.	[80]
5.	MCF-7	To elucidate the molecular mechanisms behind TQ's antiproliferative effects in breast cancer by analyzing proteome-level changes.	MCF-7 cells were treated with 15 µM TQ for 48 h, Proteins from treated and untreated (control) groups were isolated and analyzed with different techniques.	TQ significantly impacted crucial mechanisms such as carbon metabolism, amino acid biosynthesis, protein synthesis, and the citrate cycle, essential for metabolic reprogramming. Identified TQ's novel molecular targets associated with metabolic reprogramming.	[81]
6.	Female 57BL/6 mice	To investigate the impact of TQ on metabolic function of the mammary gland and ovary through the reproductive life in an animal model of obesity.	Female C57BL/6 mice were subjected to High Fat Diet (HFD) supplemented with TQ (10% pmm) and TQ (20% pmm),	TQ markedly decreased FBS, TQ decreased insulin and leptin levels in lactating females and in non-reproducing females. TQ reduced the effects of obesity induced metabolic dysfunction in mammary gland and ovary by activation of genes involved in AMPK/PGC1α/SIRT1pathway	[82]
7.	HT 29, SW480 and SW620	To investigate the chemotherapeutic effects of 5-fluorouracil (5-FU), metformin (Met), and/or TQ (TQ) single/dual/triple therapies in the HT29, SW480 and SW620 colon cancer (CRC) cell lines.	Flow cytometry, Gene and protein expression by quantitative-PCR and Western blot, Colorimetric assays	Highest pro-apoptotic actions that coincided with the lowest expression of CCND1/CCND3/PCNA/survivin and the maximal increases in p21/p27/BAX/Cytochrome-C/Caspase-3 in all cell lines. Lowest expression of lactate dehydrogenase and pyruvate dehydrogenase kinase-1 with the highest expression of pyruvate dehydrogenase. Stronger modulation of the PI3K/mTOR/HIF1α oncogenic network.	[83]
8.	STZ induced diabetic rat	To examine the effect of glycemic control using TQ (TQ) on energy metabolism related enzymes in leukocytes of streptozotocin (STZ)-induced diabetic rats.	Forty male rats, 8-week-old, Biochemical parameters	Plasma glucose, cholesterol and triglycerides levels were significantly reduced after TQ treatment, whereas immunoreactive insulin (IRI) showed significant increase. Both insulin concentration and mitochondrial malate dehydrogenase (MDH) increased	[84]

caspase-3/9 activation, release of cytochrome c and down regulation of anti-apoptotic Bcl-2 proteins (Figure 6a). Moreover, thymol activated MAP3Ks, JNK and p38 that contributed to apoptosis through the ROS induction [85]. Carvacrol on the other hand inhibits MAPKs and PI3K/AKT/mTOR. The phytochemical p-cymene also causes apoptosis in cancer cells by suppressing expression of autophagy-related proteins and mRNA including PI3K, AKT, and mTOR in bladder cancer cells (Figure 6b). In human fibrosarcoma cells it found to inhibit the metalloproteinase 9 (MMP9) expression and preventing the metastasis [86].

Pharmacokinetics of TQ

The TQ has excellent broad-spectrum activity on physiological metabolism of cancer cells and microbial organisms [79, 81-83]. Meanwhile, it is inevitably facing significant difficulties on formulation liabilities. It is sparingly soluble in water, unstable under pH and light conditions, and undergoes extensive first-pass metabolism. These characters made it hard for oral exposure shorten half- life and require a repeatedly highlighted in pharmacology and stability reviews and underpin the drive toward enabling delivery systems. Several advancements have been achieved through unequalled research work

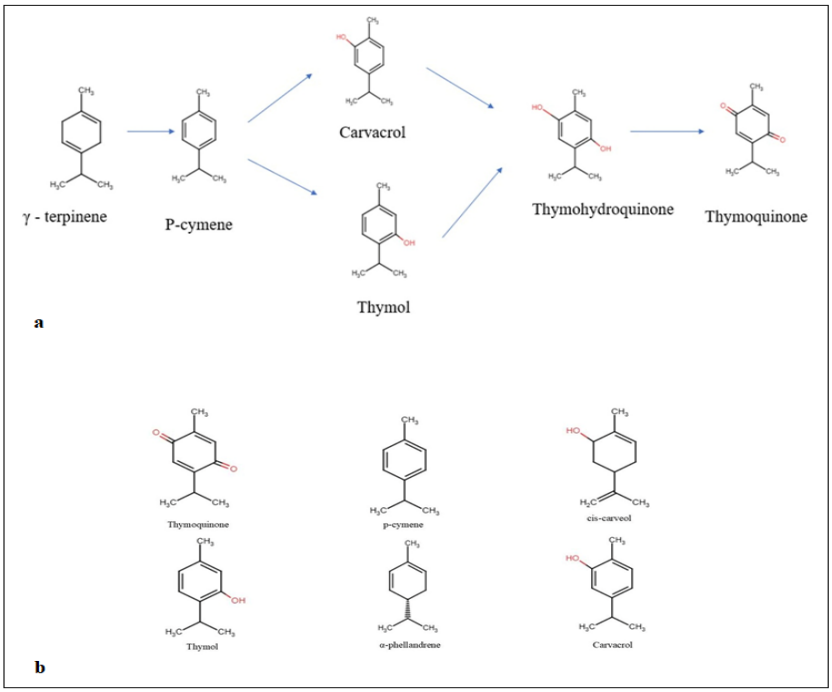

Figure 6. a. Formation of Different Phytochemicals Present in Nigella Sativa and Final Conversion into TQ. b. Different phytochemicals present in Nigella sativa with their chemical structure

on TQ [75, 76, 80, 87, 88]. Several types of lipid nano carriers have been raised and help in its extended systemic exposure and tissue distribution. Various encapsulation methods, including usage of nano- structured lipid carriers increased its bioavailability and bio-distribution on rats. These methods also help in overcoming the hurdles on dissolution and first- pass limitations. Developed self- nano emulsifying drug delivery systems achieve four- fold increased delivery orally compared to the traditional ones. Nano- scale droplets with TQs improved intestinal presentation and lymphatic uptake [89, 90]. The formulation of the delivery systems for TQ are characterized for overcoming aqueous solubility with parental and or high- payload oral systems. Inhibition of auto photo degradation of the TQ also been achieved for improving the storage and gut transit. Inclusion of cyclo-dextrin complex (e.g., HP-β-CD, SBE-β-CD), oil/ lipid-based nanoparticles, co-surfactant systems enhanced the TQ solubility, stability, and exposure and raised apparent aqueous solubility and can stabilize the quinone during processing and release [91]. The advancement such as targeted (Hyaluronic acid (HA)–decorated nanoparticles for CD44 overexpression) and or stimulus- responsive delivery (viz., acidic extracellular pH (~6.5) and elevated intracellular glutathione to trigger on-site TQ release) switched properties inside tumors for deeper penetration and on-demand release. Hence, TQ's poor solubility and instability are solvable with contemporary delivery science. The most mature paths are SNEDDS/SEDDS and lipid nanocarriers for systemic exposure, and HA-decorated or pH/redox-responsive nanoparticles for targeted, TME-adapted release together providing a realistic translational bridge from promising pharmacology to clinical testing [92].

Microtubules are the main targets for anticancer drugs and are available currently. TQ, was shown to be a Microtubule-Targeting agent (MTA) for arresting the proliferation of different cell lines. The tubulin arrest occurred in mitosis phase of G2/M cell cycle which was evident in human non-small lung epithelial cells (A549). On microtubule TQ depolymerized and disrupted mitotic spindle in A549 cell lines. This was later followed by apoptosis which led to death of cells (IC50 value of ~10 μM) [93]. On these cancer cells TQ showed inhibition of hetero-dimerization of the tubulin. Tubulin was inhibited by attaching to tubulin heterodimers that are localized at a single location and preventing polymerization. TQ binds to tubulin in a temporal manner, as shown by a tryptophan fluorescence technique [93]. According to an artificial insilico modelling research, TQ may bind tubulin at or close to the colchicine binding site. Experimentally it was proved by the modified Dixon plot analysis. The TQ and colchicine competed for tubulin binding, with a Ki of 1.9 μM. These results showed that TQ had efficient anti-cancer activity on human non-small lung epithelial cells (A549)

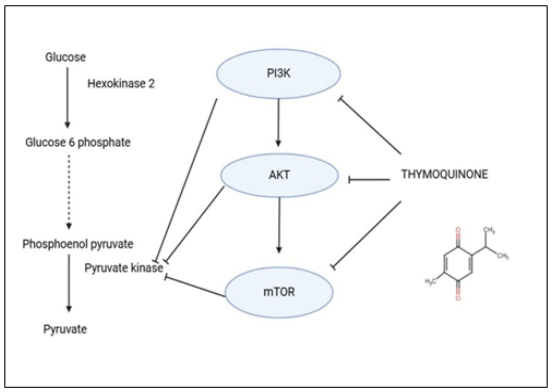

Figure 7. TQ was Shown to Inhibit PI3K-AKT-mTOR

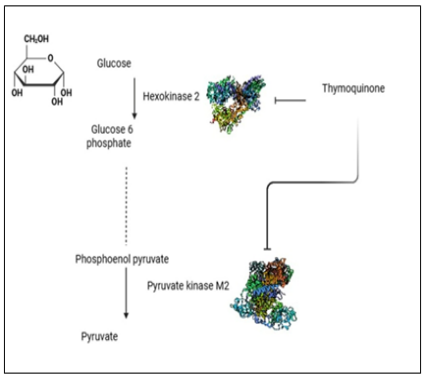

Figure 8. The Enzymes Inhibition by TQ in Glycolytic Pathways.

in different signaling pathways [94].

Action of TQ on pyruvate metabolism

TQ was also shown to regulate the pyruvate metabolisms on different cancer cells (Figure 7). TQ also could inhibit pyruvate kinase M2, that one of the prime enzymes of cancer cells predominately via PI3K-AKT Pathway inhibition [23]. PKM2 regulated the glucose uptake and its subsequent metabolism on cancer cells, TQ was shown to inhibit the glucose uptake and lactate formation. TQ treatment reduced the expression of HK2 in SW480 [84, 96] and HCT116 [79, 96] cells. Reduction in HK2 levels upon TQ treatment coincided with significant inhibition in PI3K-AKT was demonstrated in pediatric osteosarcomas [97]. When selective pharmacologic inhibitor (LY294002) of PI3K was used significant reduction in HK2 levels concomitant to PI3K-AKT inhibition was observed [98]. Similarly, TQ was shown to inhibit pyruvate dehydrogenase kinase-3 on in silico and in vitro studies also [99].

TQ on pyruvate pathways of CAF

TQ can contrarily induce oxidative stress in cancer cells, which may affect the regulation of glycolytic enzymes. TQ could affect the signaling pathways like PI3K/Akt that regulate glycolysis in CAFs [64]. Very few studies, at present, carried on the role of TQ on the epigenetic modifications related to pyruvate metabolism [23, 69, 100]. Traditional mode of treatments especially for cancer, with appropriate technological advancements may be more effective when compounds like TQ that target CAF metabolic interruption are used in their purified form [76, 78] (Figure 8).

Similar to TQ, few of its related compounds were also shown to have bioactivity on CAFs.

Similar compound, Shikonin, a naphthoquinone compound, also reversed the effect of cancer-associated fibroblast of pancreatic cancer cells with the induced with gemcitabine resistance. The shikonin mediated the suppression of monocarboxylate transporter 4 and reprogrammed the CAFs. Further, it also been showed to inhibit CAF-induced Peroxisome proliferator-activated receptor gamma (PPARγ) coactivator 1-alpha (PGC-1α) expression, nuclear localization, and interaction with estrogen-related receptor alpha (ERRα) in triple-negative breast cancer (TNBC) [101]. Similarly, Juglone another naphthoquinone, reduced the collagen production by CAFs in pancreatic ductal adenocarcinoma. It has cytotoxic effects on podoplanin (PDPN) stained CAFs having activation markers such as alpha-smooth muscle actin (α-SMA), vimentin [102].

Several natural compounds, including TQ, were showed to inhibit the auto and or paracrine signals generated by the cancer cells on TME. Stromal fibroblasts are converted and maintained in to a state of glycolytic by the oxidative and inflammatory clues rendered by cancer microenvironment through paracrine and or autocrine signalling pathways [48]. At this stage, the converted lactate of those CAFs is used to feed cancer cells rather than by themselves. CAFs are termed as lactate exporters and cancer cells are acting as importers; this is achieved via expression of MCT1 to MCT4 (SLC16A3), from CAFs to cancer cells, respectively. Irrespective of types, almost all of the cancers use CAFs as their lactate exporters and use this reverse Warburg effects. Meanwhile, higher expression of MCT4 made them as a risky biomarker [65, 66, 29].

At basic level CAFs tend to shut off the mitochondrial glucose oxidation and increase the usage of glycolytic enzymes and transporters (e.g., GLUT1, HK2, LDHA) [84]. This creates a steady efflux of the lactate in to tumor mileu and eventually acidifies the TME. This acidification results in promotion of the tumor angiogenesis, invasion, and or immune evasion also. The cancer cells oxidize the lactate (occasionally the pyruvate) as their primary carbon source on nutrient or oxygen stress with the help of MCT1. The MCT1 acts as a lactate influx, blocking lactate usage can force metabolic shifts and reduce fitness of oxidative cancer sub-clones [71] (Figure 8). CAFs are also secreting the pyruvate and cancer cells use their monocarboxylate transporters and stimulate the tumor survival and growth, without. Thus, this stromal paracrine nutrition strongly supports the cancer growth, even without any physical contact. In lymphoma models, CAF-secreted pyruvate enhanced tumor cell survival and the effect was abrogated by MCT inhibition, demonstrating transporter-dependent metabolic coupling. Collectively, these data support a picture in which glycolytic, MCT4-high CAFs sustain OXPHOS-competent cancer cells via lactate/pyruvate shuttling, with clear therapeutic leverage points at LDH-A, MCT1, MCT4, and the upstream HIF-1/PDK–PDH gate that decides whether pyruvate is oxidized or reduced [22].

HIF-1α and CAFs: Thymoquinone

HIF-1α is one of the master switches for regulating the glycolysis and the fate of pyruvate oxidation. It phosphorylates and trans-activates the PDK1, and also inhibits the pyruvate dehydrogenase (PDH). This prohibits the pyruvate from mitochondria and enhances the NAD+ regeneration from lactate [74]. Several studies showed that TQ down regulated the glycolytic target genes such as GLUT1 and PDK1 on hypoxic conditions [99]. In renal cells, TQ killed hypoxic cells correlated with the glycolysis and adaptation. In CAFs, where glycolysis is partly driven by HIF-1, TQ is expected to decrease

Table 6. Drugs that Modulate Reverse Warburg Effect

Sl. No.	Type of inhibitor	Example	Mechanism of action	References
1	NF-κB/HIF-1α suppression	TQ	ROS modulation in CAFs	[75]
2	HIF-1α inhibitors	3,3'-Diindolylmethane (DIM), Curcumin	Reduces glycolytic reprogramming in CAFs	[64]
3	LDHA inhibitors	Galloflavin	Decrease lactate secretion from CAFs	[22, 23]
4	MCT1 inhibitor	AZD3965	Inhibit lactate uptake by tumor cells	[67]

glycolysis and thereby reduce pyruvate levels. PDK1 mediates the pyruvate pathway by phosphorylating the PDH- E1α through the PDH and reduction in the presence of LDH-A pathways. Even though, effects on TQ on hypoxia were showed by several studies, its establishment concepts with CAFs are on basic level. Dichloroacetate was shown to inhibit the PDK and opened the PDH gate and well- established in hypoxic literature. Similar to logic, TQ could also open the PDH gate by decreasing the PDH-E1α phosphorylation. TQ appears to push CAFs in a similar direction through upstream transcriptional/ redox control. Net effect is less lactate overflow and more mitochondrial oxidation [32, 33, 35].

TQ was also shown to potently activate the Nrf2 in various levels, by increasing the HO-1 and NQO1 and halting the oxidative stress. In other hand, ROS stabilizes and promotes the HIF-1α and increasing the glycolysis on specific conditions, called as "pseudo- hypoxia". Hence, TQ could reverts the ROS suppression and create a negative- feedback for anti-glycolytic shift. Further, if the TQ shuts down the HIF-1 targets, it also could reduce the pyruvate and lactate and eventually inhibit the MCT4 transportation on cancer cells [48, 49, 74]. Coupled to reduced need for lactate export, MCT4 expression and flux should also decline a meaningful change because MCT4-high CAFs are a hallmark of the reverse Warburg phenotype and correlate with aggressive disease [52, 53]. However, several studies on TQ activity have been shown that TQ could suppress HIF-1 related glycolysis in tumor cells, irrespective of their origin and or types. Hence, it may inhibit also MCT4 and dampened LDH- A/ MCT4 axis. This might make starvation of the cancer cells by inhibiting stromal nutrition, and eventual reduction of TME acidification that fosters invasion and immunosuppression. The downstream expectation is lower lactate production (LDH-A) and reduced lactate efflux (MCT4) from CAFs [22, 23, 103]. On the cancer cell side, with less exogenous lactate/pyruvate coming from stroma, oxidative tumor cells may lose a preferred fuel, becoming more dependent on glucose and potentially less invasive; in some settings, blocking lactate usage forces cells into less efficient metabolic states and can reduce metastatic traits. MCT blockade should phenocopy aspects of TQ in co-culture. Though the direct evidence is still not available, this could be a mechanistic view of the TQ action on the CAFs and their pyruvate metabolism and requires a molecular level analysis in future [65]. Many of the direct evidences for TQ metabolic actions could derive from the cancer studies, but, rarely available within the CAFs milieu. Hence, while the direction of effect is well supported CAF-specific endpoints, especially MCT4 modulation, should be experimentally confirmed.

Clinical perspective of TQ on pyruvate pathways of CAFs

Translating knowledge on the modulation of pyruvate metabolism from bench to bedside is important, as CAFs produce lactate that cancer cells utilize to generate ATP and meet their energy demands [71]. Pyruvate is converted into lactate in the presence of LDH-A and HIF-1α upregulates the transporter MCT4, which export lactate from CAFs into extracellular matrix of TME [67]. Targeting pyruvate-lactate loop is relevant from the clinical perspective (Table 6). TQ downregulates HIF-1α, inhibit PI3K/AKT/mTOR signaling pathway, suppresses enzymes such as PDHK1/PDK1, LDHA and increasing PDH, thus may reduce lactate output from CAF [74]. Even though the evidence for the effects of TQ on pyruvate metabolism of CAFs are lacking, TQ can be considered as a promising compound that can be used in future anticancer therapy by modulating the same pathways [76, 78, 89, 104].

In conclusion, through our deep literature search we narrate this review to conclude that TQ which is a major compound derived of Nigella sativa has significant interruption role in glycolytic pathways especially against the hexokinase 2 and pyruvate kinase M2. More over the consequent effects are extending to other pathways that are linked to glycolytic pathways such as IP3-AKT-mTOR pathways. At this juncture the tumor microenvironment should be paid keen attention to. Cancer-associated fibroblasts are crucial because they supply nutrition to cancer cells and regulate pyruvate metabolism in them, which are potentially influenced by TQ. Our review further narrows down and pinpoints the role of pyruvate metabolism in CAFs in lymphomas and highlights the effect of TQ on these specific pathways. Further studies with a multidirectional approach should explore the anticancer and antiproliferation properties of TQ, specifically against CAFs, in the field of cancer therapeutics.

Acknowledgments

Statement of Transparency and Principles

• The authors declare no conflict of interest.

• The study was approved by the Research Ethics Committee of the authors' affiliated institution.

• The study data are available upon reasonable request.

• All authors contributed to the implementation of this research.

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