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# CANCER MANAGEMENT BEYOND GENETICS

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## ABSTRACT

Cancer arise from a breakdown in cellular regulation, resulting in uncontrolled proliferation of cells that persists even after the original growth stimuli have stopped. While benign tumors remain localized, malignant forms which is termed as cancer has invasive and metastatic potential. The underlying driver of this uncontrolled cell proliferation are genetic mutations and epigenetic modulation. Genetic mutation serve as the initiators of oncogenesis, disrupting key regulatory genes and promoting continuous cell division. However, the long-term survival, adaptation, and progression of cancer cells are driven by epigenetic modifications. These epigenetic regulators are the components of tumor microenvironment (TME), which supports cancer cell plasticity, immune evasion, and therapeutic resistance. While genetic mutations may initiate cancer, the persistence and progression of the disease are largely governed by TME-mediated epigenetic modulation. This review explores the contribution of TME in sustaining cell proliferation and malignancy and highlights emerging strategies for cancer management through the modulation of the tumor microenvironment.

**KEYWORDS:** Solid tumor, TME, Epigenetic modulation, Physiological adaptation, Disease modification.

## INTRODUCTION

Cancer progression is not solely driven by genetic mutations; rather, it is strongly influenced by the tumor microenvironment (TME), which plays a critical role in supporting cancer cell survival and proliferation. The entire physiological system contributes to cancer development

by transforming normal biological conditions into a cancer-promoting milieu. This includes continuous cell division (uncontrolled cell proliferation), formation of new blood vessels (neo angiogenesis) to nourish tumor cells, invasion into distant organs (metastasis), evasion of immune surveillance (immune evasion), and metabolic reprogramming (Warburg effect). These alterations are not exclusively governed by genetic abnormalities. Instead, they reflect a physiological adaptation that facilitates tumor progression, suggesting that chronic stress is a primary driver, ultimately leading to both genetic disruption and a supportive environment for malignancy. Current treatment modalities, including chemotherapy, radiotherapy, and surgery, are primarily designed to eliminate cancer cells by killing or attacking rather focusing on rate of cell division. However, these interventions often impose additional stress on the physiological system, potentially exacerbating tumor aggressiveness, resistance, and recurrence.[1,2,3] This perspective suggests that whole living system counter act to the chronic stress via cancer development. So treating cancer effectively requires more than killing cells**.** By targeting the TME we may prevent cancer from adapting and resisting treatment offering a decrease in rate of continuous cell division and more sustainable path toward long-term control.[4,5,6] This review examines the key components of the tumor microenvironment (TME) and explores therapeutic strategies aimed at modulating this supportive niche. By targeting the physiological support systems tumors depend on, we may shift cancer therapy from symptom control to disease modification.

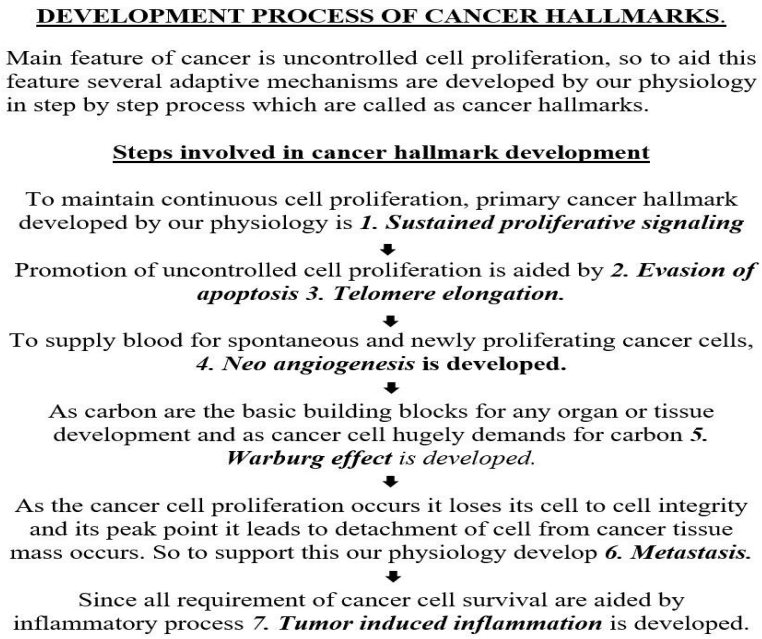


**Fig 1.**

## MECHANISM OF CANCER HALLMARK DEVELOPMENT AND ITS OUTCOMES

This is explored to target the TME factors which are formed by cancer hallmark pathway to manage cancer.

### 1. SUSTAINED PROLIFERATIVE SIGNALING AND EVASION OF APOPTOSIS

The PI3K/AKT/mTOR axis is a intracellular signaling pathway that regulates various cellular functions such as growth, survival, and metabolism. Activation begins when external stimuli like growth factors IGF, EGF etc.,) bind to specific cell surface receptors, triggering a cascade that leads to the activation of AKT and downstream mTOR complexes. These downstream activation enhance protein synthesis, inhibit apoptosis, and promote cell cycle progression functions that are often controlled by cancer cells to support unchecked growth and survival.

### 1.1. Mechanism of action

The PI3K/AKT/mTOR signaling pathway gets triggered when growth factors like insulin, IGF-1, or EGF bind to specific receptors on the surface of the cell—these receptors are typically either receptor tyrosine kinases (RTKs) or G protein-coupled receptors (GPCRs). Once these receptors are activated, they, in turn, activate a group of enzymes called Class I PI3Ks. Activated PI3Ks then modify a lipid molecule in the inner layer of the plasma membrane, converting phosphatidylinositol-4,5-bisphosphate ($PIP_2$ ) into a new signaling molecule called phosphatidylinositol-3,4,5-trisphosphate ($PIP_3$ ). This $PIP_3$ acts like a signal flare, attracting proteins with pleckstrin homology (PH) domains—most importantly AKT and PDK1—to the membrane. Once at the membrane, PDK1 begins the activation process by phosphorylating AKT at a specific amino acid (Thr308 in AKT1, Thr309 in AKT2). A second activation step is carried out by the mTORC2 complex, which adds another phosphate to AKT (at Ser473 or Ser474), fully activating it. Fully active AKT then begins to influence several key cellular processes. It helps turn on mTORC1 by modifying TSC2 and PRAS40, both of which usually act as brakes on mTORC1 activity. When these brakes are lifted, mTORC1 becomes active and starts promoting cell growth and metabolism. AKT also plays a key role in cell survival. It inhibits proteins like Bad and caspase-9 that would otherwise trigger apoptosis (programmed cell death). It also keeps FOXO transcription factors out of the nucleus, preventing them from activating genes that slow down the cell cycle or encourage cell death, such as p21 and p27. In parallel, AKT supports inflammatory and survival responses by activating the NF-κB pathway through IKK phosphorylation. As a

downstream effect, mTORC1 activates key proteins like S6K1 and 4E-BP1. These proteins enhance the cell's ability to make proteins: S6K1 boosts the production of ribosomal components, while phosphorylation of 4E-BP1 releases eIF4E, a factor essential for initiating translation. Together, these actions promote cap-dependent protein synthesis and support rapid cell proliferation.[7,8,9,10]

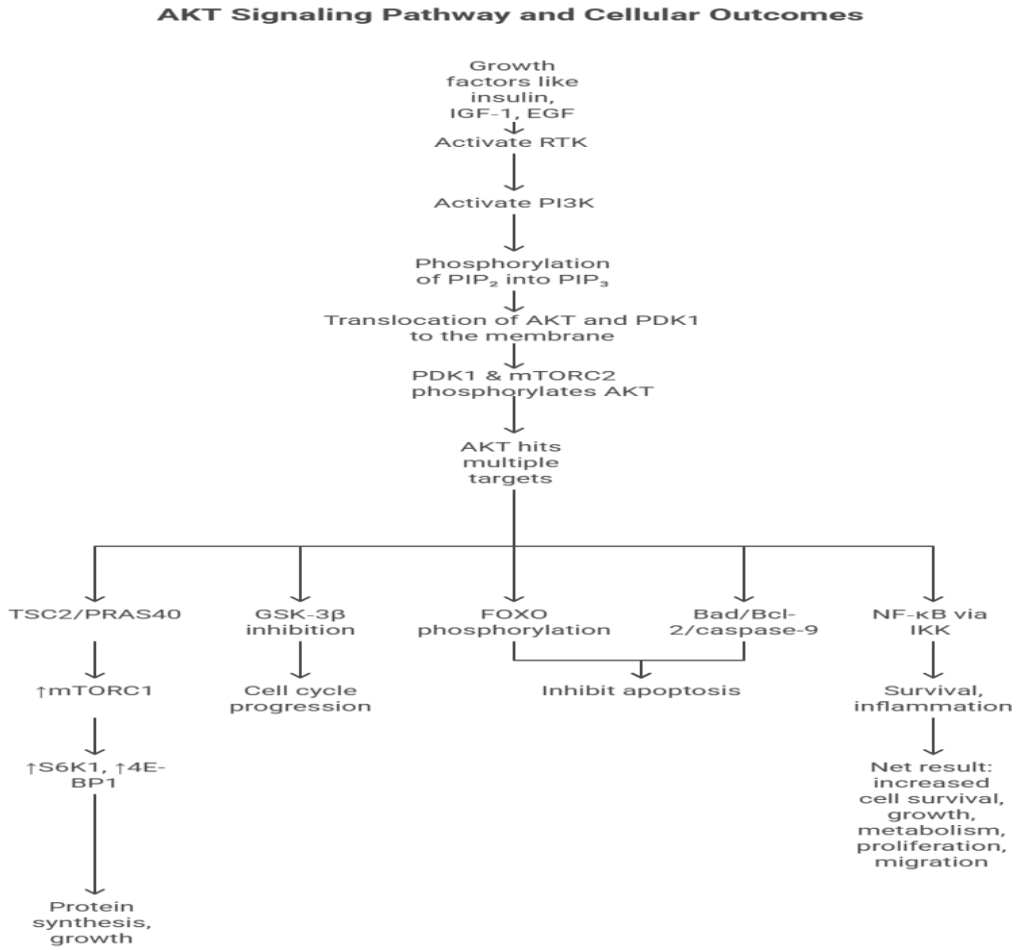


**Fig 2**

### 1.2. Outcome components of TME

- Uncontrolled cell proliferation and accumulation of pro inflammatory cytokines which developes i) *tumour induced inflammation*, ii) *neoangiogenesis* and iii) *evasion of apoptosis* as cancer hallmarks.[11,12]
- The predominant byproducts formed by uncontrolled cell proliferation in solid tumors include lactate, glutamate, fumarate and succinate. These metabolites are associated with the altered metabolic processes of cancer cells and play significant roles in tumor survival and progression.[13,14]

- Presence of hypoxia induced factors (HIF) HIF-1 and HIF-2, HIF-α.[15,16]
- Presence of Myeloid Derived Suppressor Cell (MDSC).[15,17]
- Increased cholesterol level and adipokinin.[18,19]
- SQLE (Sqalene Monooxygenase) and MYC (myelocytomatosis).[20]
- Presence of fibroblast, cytokine, chemokine, T cells, m2 macrophages, other immune cells.[21,22]
- Rich in collagen, proteoglycans, hyaluronic acid, laminins, fibronectin.[23,24]

## 2. WARBURG EFFECT

Warburg effect was first observed by Otto Heinrich Warburg. Anaerobic glycolysis utilization by cancer cells in the presence of abundant oxygen is called Warburg effect. This change in metabolic pathway is done to store glucose and carbon which are the basic building blocks for anabolic activity of cancer cell proliferation.[25,26]

### 2.1. Mechanism of action

Cancer cells frequently reprogram their metabolism by depending more on glycolysis than on oxidative phosphorylation, even in the presence of sufficient oxygen. This metabolic shift, known as the Warburg effect, enables them to rapidly break down glucose into lactate. Although this pathway produces less energy than mitochondrial respiration, it supports the high demands of rapidly dividing cells by providing both quick ATP and the raw materials needed for biosynthesis. This metabolic adaptation is often driven by genetic and molecular changes, including the activation of oncogenes like MYC and components of the PI3K/AKT/mTOR pathway. In addition, low oxygen conditions in the tumor microenvironment activate hypoxia-inducible factor 1-alpha (HIF-1α), which increases the production of glucose transporters and enzymes involved in glycolysis while suppressing mitochondrial function. As a result of these changes, lactate builds up in the tumor environment, creating an acidic setting that promotes tissue invasion and helps cancer cells avoid detection and destruction by the immune system.[27,28,29]

### 2.2. Outcomes components of TME

- As the end product of anaerobic glycolysis is lactic acid, lactic acid accumulates in our body. This makes the cancer environment acidic which favors tumor progression.[30,31]

Mechanism of acidic environment contributing tumor progression

**i. Cell proliferation**

Acidity induces toxicity on normal cells and tumor cells are resistant to acid stress. As the normal cell dies, tumor cell continue to proliferate and invade the open space. Acidity also induces the degradation of extracellular matrix through the release and activation of protease, such as cathepsin B and matrix metalloproteases (MMPs) such as MMP-1, 2, 9, which involves in local invasion and tissue remodeling.[32,33]

**ii. Induction of Stem Cell-Like Features**

Exposure to acidosis stimulates the development of cancer stem cell phenotypes by increasing stem cell marker expression and secretion of angiogenic factors such as vascular endothelial growth factor (VEGF), which promotes neovascularization and further tumor growth.[33]

**iii. Promotion of angiogenesis**

Acidic conditions in the tumor microenvironment inhibit mitochondrial oxidative phosphorylation (OXPHOS), reducing cellular oxygen consumption and leading to a pseudo-hypoxic state. This environment also triggers abnormal angiogenesis, resulting in dysfunctional blood vessels that impair effective oxygen delivery, thereby causing true hypoxia**.** Together, acid-induced hypoxia and the activation of HIF promote the formation of new, though often abnormal, blood vessels. This neovascularization enhances nutrient supply and waste removal, ultimately supporting tumor growth and progression.[33]

- **Increased level of glutamine[34,35]**

Mechanism of glutamine contributing tumor progression

Glutamine serves wide range of nutrient for cancer cells, providing both carbon and nitrogen necessary for biosynthetic processes.[36,37,38] Many tumors exhibit glutamine addiction, relying on glutaminase enzymes to convert glutamine into glutamate and downstream metabolites. Targeting glutamine metabolism disrupts this dependency, making it a promising therapeutic strategy.[39,40]

- **Accumulation of Cancer Associated Fibroblast (CAF)**

It facilitate reverse Warburg effect.[41] and stromal- cancer metabolic coupling. nf-kb and HIF-1αA induce Mono carboxylate transferase-4 (MCT-4) is highly expressed in CAF and which aids release of catabolite from adjacent stromal cells and MCT-1 is highly expressed in

cancer subtypes which is responsible for catabolite uptake. MCT-1 are induced by MYC and TP53 Induced Glycolysis and Apoptosis Regulator (TIGAR).[42]

- Increased oxygen supply by stromal cell to tumor cell which stimulates tumor growth.[43]
- Increased expression of $p53^{mut.}$[44] and NADH accumulation.[45]

## 3. METASTASIS

Metastasis is defined as the process by which cancer cell migrate from their original location to other parts of the body. This occurs due to loss of cell integrity as there is uncontrolled cell proliferation and disorganized cellular arrangement.[46]

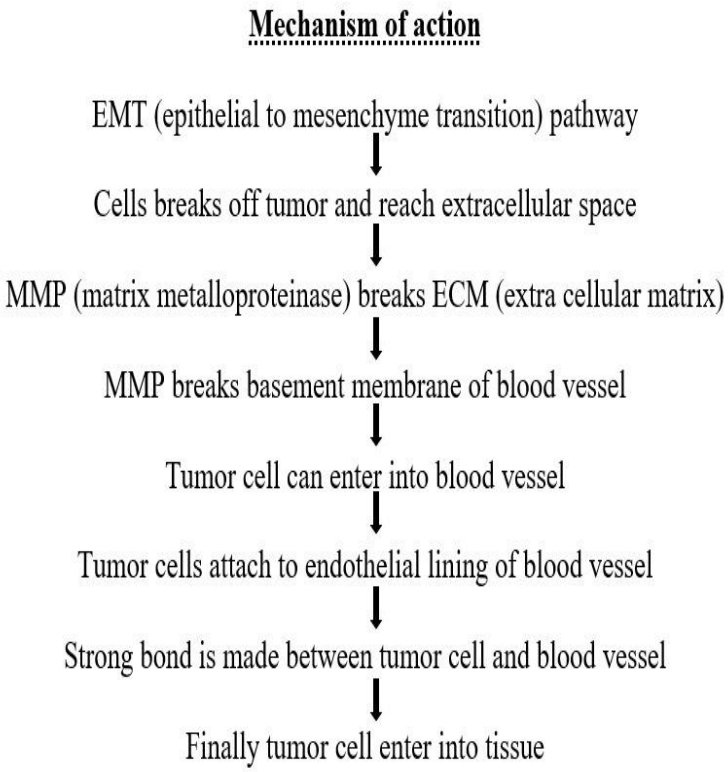


**Fig 3.**

### 3.1. Outcome components of TME

- **EXOSOMES**

Low oxygen conditions in solid tumors stimulate the release of exosomes, tiny vesicles that act as carriers of molecular signals between cancer and stromal cells. These exosomes facilitate several malignant behaviors, including tissue invasion, resistance to treatment, and

immune modulation. By transporting molecules like PD-L1 and various RNA species, they help create a microenvironment that supports tumor progression under hypoxic stress.[47,48]

- **M2 MACROPHAGES**

Within the tumor microenvironment, macrophages can undergo functional polarization into different phenotypes. The M2 subtype, commonly referred to as tumor-associated macrophages (TAMs), plays a key role in promoting tumor growth and immune suppression. These cells release pro- tumoral cytokines, enhance blood vessel formation, and suppress cytotoxic immune responses contributing significantly to metastasis and therapy resistance.[49] Over 80% of clinical studies shows that m2-like macrophage density associated with cancer progression.[50]

**Functions of M2 macrophage**

**i. Promotion of Tumor Growth**

M2 macrophages release various cytokines and growth factors that support tumor cell survival and proliferation. For instance, they can enhance the expression of (VEGF), which is crucial for angiogenesis.[51,52]

**ii. Facilitation of metastasis**

M2 macrophages can influence the migration and invasion of cancer cells. Their interaction with tumor cells can lead to the expression of genes associated with stemness and drug resistance, effectively transforming them into a more aggressive state that promotes metastasis.[53,54]

**iii. Regulation of Immune Responses**

M2 macrophages can suppress the activity of cytotoxic T cells and other immune cells, creating an immunosuppressive niche that allows tumors to evade immune detection.[55]

**iv. Influence of Tumor Microenvironment**

The TME, characterized by factors such as hypoxia, can further drive the polarization of macrophages toward the M2 phenotype. For example, hypoxic conditions have been shown to enhance M2 polarization, thereby exacerbating tumor progression.[56]

- **PRESENCE OF VARIOUS STROMAL CELLS[57]**

**i. Carcinoma-associated fibroblasts (CAFs)**

Cancer-associated fibroblasts (CAFs) are abundant stromal cells that play a critical role in modulating the tumor microenvironment. These fibroblasts secrete growth factors, remodel the extracellular matrix, and facilitate angiogenesis. Importantly, they engage in metabolic coupling with cancer cells, often supplying nutrients and signaling molecules that enhance tumor survival and invasiveness.[58]

ii. Presence of MSC (mesenchymal stromal cells), T and b lymphocytes, endothelial cells, pericytes.

- **ADIPOCYTES**

Adipocyte Interaction with Tumor Cells

Adipocytes and tumor cells engage in complex interactions that influence the tumor microenvironment (TME), promoting cancer progression and metastasis.

**i. Cytokine Secretion**

Adipocytes secrete various cytokines (e.g., IL-6, IL-8, TNF-α) that contribute to the epithelial-mesenchymal transition (EMT) in cancer cells, facilitating their invasion and metastatic potential.[59,60]

**ii. Macrophage Polarization**

Adipose tissue macrophages (ATMs) can polarize between M1 (anti-tumor) and M2 (pro-tumor) phenotypes. In the presence of tumor cells and inflammatory signals, they often shift towards the M2 phenotype, which supports tumor growth and metastasis.[61,62]

**iii. Extracellular Matrix (ECM) Modulation**

Tumor cells can degrade the ECM and recruit immune cells, including macrophages, which then create a supportive microenvironment for cancer progression.[63,64]

**iv. Chronic Inflammation**

The inflammatory environment created by adipocytes leads to chronic low-grade inflammation. This condition favors the recruitment and polarization of macrophages towards the M2 phenotype, enhancing their pro-tumor activities.[65,66,67]

### 3.2. DISREGULATORY CONDITIONS IN THE TME

**i. Hypoxia**

Hypoxia is a common condition in solid tumors due to inadequate blood supply from poorly organized tumor vasculature. It leads to changes in cellular behavior, including enhanced survival, increased metastatic potential, and resistance to therapy. Under hypoxic conditions, tumor cells secrete higher amounts of exosomes, which further modulate the TME and promote drug resistance.[68,69]

**ii.** Altered Immune Environment

The presence of immune checkpoint molecules like B7-H3 in the TME correlates with decreased T-cell infiltration and function, leading to poor prognosis and resistance to therapies.[70]

## 4. CANCER- STRESS RELATIONSHIP

### 4.1 Stress –homeostasis relationship

According to physiology, stress is considered as a factor which alters or damage the homeostatic condition of the body and physiology have the capability to develop several adaptive features to restore homeostasis. Restoration process which carry on by the physiology itself will lead to several disease and pathological conditions when exposed to chronic stress.[71,72,73,74] One of the restoring process by the physiology is inflammatory response in which restore damaged or dead cell by new cell proliferation,[75,76,77] In case of chronic inflammation it leads to cancer.[77,78,79,80]

### 4.11. Inflammation

Inflammation is a complex biological response of body tissues to harmful stimuli, such as pathogens, damaged cells, or irritants. It is a critical component of the innate immune response, serving as a defense mechanism aimed at eliminating the initial cause of cell injury, clearing out necrotic cells and tissues, and establishing a repair process.

Generally inflammatory process can be divided into three sections. Recruitment, removal, repair process. In recruitment process immune cells are gathered at injures site. In removal process pathogen and dead cells are removed by phagocytic immune cells. Finally in repair process damages tissues are regenerated by new cell proliferation.[137,138,140]

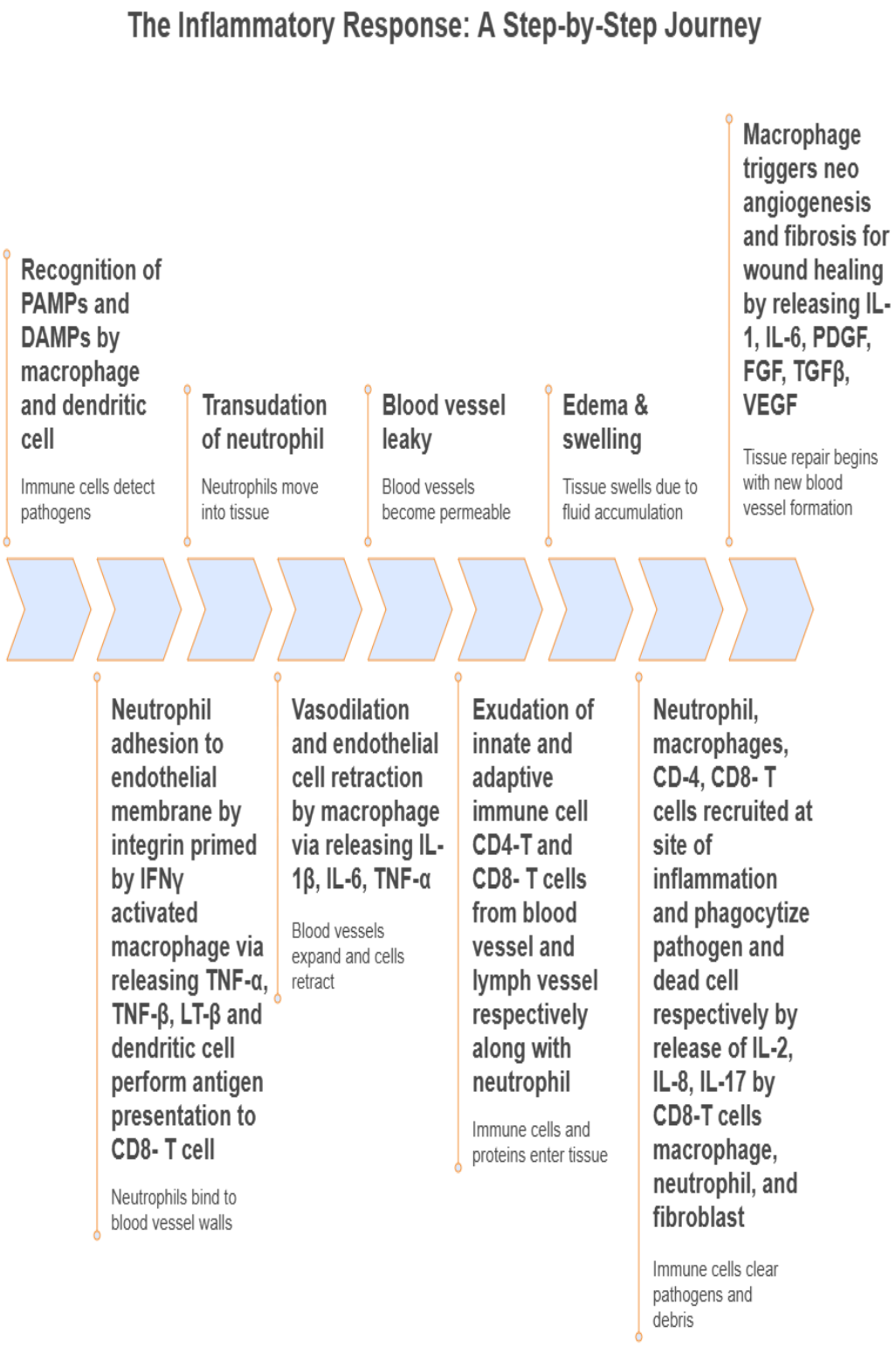
The Inflammatory Response: A Step-by-Step Journey
Recognition of PAMPs and DAMPs by macrophage and dendritic cell
Immune cells detect pathogens
Transudation of neutrophil
Neutrophils move into tissue
Blood vessel leaky
Blood vessels become permeable
Edema & swelling
Tissue swells due to fluid accumulation
Macrophage triggers neo angiogenesis and fibrosis for wound healing by releasing IL-1, IL-6, PDGF, FGF, TGFβ, VEGF
Tissue repair begins with new blood vessel formation
Neutrophil adhesion to endothelial membrane by integrin primed by IFNγ activated macrophage via releasing TNF-α, TNF-β, LT-β and dendritic cell perform antigen presentation to CD8- T cell
Neutrophils bind to blood vessel walls
Vasodilation and endothelial cell retraction by macrophage via releasing IL-1β, IL-6, TNF-α
Blood vessels expand and cells retract
Exudation of innate and adaptive immune cell CD4-T and CD8- T cells from blood vessel and lymph vessel respectively along with neutrophil
Immune cells and proteins enter tissue
Neutrophil, macrophages, CD-4, CD8- T cells recruited at site of inflammation and phagocytize pathogen and dead cell respectively by release of IL-2, IL-8, IL-17 by CD8-T cells macrophage, neutrophil, and fibroblast
Immune cells clear pathogens and debris

**Fig 4.**

4.12 **Correlation between tissue repair process of chronic inflammation and cancer:**

| ASPECT | TISSUE REPAIR PROCESS | CANCER PROGRESSION |
|---|---|---|
| **Initiation** | Triggered by injury or infection, leading to a coordinated immune response that promotes healing. | Initiated by chronic inflammation, which creates an environment conducive to tumor development |
| **Cellular Involvement** | Involves various immune cells, particularly M2 macrophage that transition from a pro-inflammatory to an anti-inflammatory state to facilitate repair | Pro-inflammatory cytokines and immune cells (e.g., macrophages, T-lymphocytes) are involved, promoting tumor growth and angiogenesis |
| **Cytokine Role** | Growth factors and cytokines are secreted to regulate tissue repair | Cytokines such as TNF-α, IL-6, and COX-2 are up regulated, contributing to inflammation and cancer progression |
| **Microenviron-ment** | The **extracellular matrix (ECM)** is remodeled to support tissue regeneration | Alterations in the ECM promote a **tumor microenvironment (TME)** that facilitates cancer cell survival and proliferation |
| **Outcome** | Successful tissue repair restores homeostasis and function | Persistent chronic inflammation can lead to malignant transformation and cancer development |
| **Pathological Changes** | Inadequate or dysregulated repair can lead to fibrosis or chronic inflammatory diseases | Chronic inflammation is associated with increased risk for various cancers due to sustained tissue damage and DNA mutations |
| **Regenerative vs. Malignant** | Regenerative inflammation aims for healing and restoration of normal function | Malignant transformation is characterized by uncontrolled cell growth and invasion |

**Fig 5.**

### 4.13. Cancer–Stress Relationship

Chronic stress triggers physiological responses that include both acute and chronic inflammation. This inflammatory response initiates tissue repair mechanisms, which in turn remodel the extracellular matrix (ECM). Such ECM remodeling creates a supportive environment for tumor growth and progression.

### 4.14. Outcomes components of TME

Cortisol, a stress-related hormone, plays a complex role in cancer biology. Elevated levels of cortisol in cancer patients are linked to development of maladaptive tissue repair environment

that forms immunosuppressive tumor microenvironment. Cortisol can influence macrophage polarization, favoring the tumor-promoting M2 phenotype, and contribute to the evasion of immune surveillance. Therapeutically modulating cortisol pathways may thus offer a route to restore immune function and enhance treatment responsiveness.[81,82,83]

## CANCER THERAPY APPROACH

Based on the analysis of cancer hallmarks and their associated components within the tumor microenvironment (TME), it is evident that many of these elements, particularly those involving immune cells, closely resemble the tissue repair processes seen during inflammation. This resemblance supports the perspective that cancer may, in part, represent a maladaptive defense mechanism. Therefore, the therapeutic strategy to alter TME are orchestrated into series of therapies which focus on reprogramming the pathological TME into a normalized, homeostatic environment that supports tissue health rather than tumor progression.

## STEP 1: HORMONAL MODULATION AS AN INITIAL STRATEGY TO REPROGRAM THE TUMOR MICROENVIRONMENT

Emerging perspectives view cancer not merely as a pathological process but as a maladaptive defense mechanism wherein the body attempts to restore tissue integrity through chronic activation of repair and survival pathways. To reverse this pathological state, one potential therapeutic approach involves the modulation of hormonal signaling pathways that contribute to tumor growth and the maintenance of the tumor microenvironment (TME). Key hormones implicated in tumor progression include insulin-like growth factors (IGFs).[84,85] growth hormone (GH),[86] and cortiso.[81] Among these, cortisol plays a pivotal role in shaping an immunosuppressive and anti-inflammatory surrounding within the TME, thereby facilitating immune evasion and tumor tolerance. Therapeutically targeting cortisol signaling contributes to disruption of protective niche, restore immune surveillance, and promote a shift toward a more immunogenic and therapeutically responsive environment.

## ROLE OF CORTISOL IN CANCER

Cortisol, a key glucocorticoid steroid hormone, is predominantly secreted in response to physiological stress and stimulate anti-inflammatory mechanisms and tissue repair processes. One of the critical pathways through which cortisol functions involves the induction of M2c macrophage polarization, contributing to immune modulation and the maintenance of the tumor microenvironment.[87] Elevated cortisol levels are commonly observed in cancer

patients, indicating its association with the stress-related pathophysiology of cancer.[88,89,90] As cancer is increasingly recognized as a sterile inflammatory condition (driven by damage-associated molecular patterns (DAMPs)). In this context, anti-stress agents that antagonize cortisol's immunosuppressive effects have emerged as promising candidates for anticancer therapy, offering potential to modulate tumor progression through the reprogramming of immune responses.

## SOME OF NATURAL SOURCES USED TO TARGET CORTISOL

### i. Ocimum sanctum (Holy Basil)

Ocimum sanctum, also known as holy basil, has been found to play a significant role in managing stress by naturally reducing cortisol levels. This effect is believed to occur through its ability to inhibit Corticotropin-Releasing Hormone Receptor 1 (CRHR1), a critical component in the body's stress signaling system. Experimental findings have shown that individuals or animals receiving Ocimum sanctum exhibited not only lower cortisol levels but also improvements in physical and behavioral markers of stress, such as healthier weight gain and reduced immobility in stress-related tests. These outcomes support its use as a potential hormonal balancer herb for promoting stress restoration.[91]

### ii. Scutellaria lateriflora (Skullcap)

Scutellaria lateriflora extracts have been found to significantly suppress cortisol production in laboratory cell studies. The reduction in cortisol ranged from 58% to 91%, depending on the concentration used. These findings suggest that this plant may hold promise as a natural dietary component for helping the body manage stress linked to elevated cortisol levels.[92]

### iii. Dark Tea Polysaccharide (DTP)

Research indicates that Dark Tea Polysaccharide (DTP) can interfere with the conversion of cortisone into cortisol in human skin cells. By influencing this hormonal pathway, DTP may contribute to the relief of stress-induced skin issues, suggesting its possible benefits not only for skin health but also for overall stress regulation in the body.[93]

## STEP 2: TARGETING TUMOR-STROMA INTERACTIONS

As the progression of cancer is heavily influenced by its interaction with stromal cells, disrupting this tumor–stromal communication is essential. Antagonizing these interactions can impair the supportive environment that tumors rely on, thereby limiting cancer growth and progression.

TUMOR- STROMAL CELL COMMUNICATION PATHWAYS

**Direct Cell-Cell Communication**

Direct communication occurs through physical contact between cells, which can involve several mechanisms.

**Juxtacrine Signaling**

It is a type of direct cell-cell communication. This involves adjacent cells communicating through direct contact, often mediated by cell adhesion molecules or receptors on their surfaces. This type of signaling is essential for maintaining tissue architecture and function.[94,95]

**Various components of juxtacrine signaling**

**i. Connexins**

Connexins (Cxs) are integral membrane proteins that form gap junctions and hemi channels. Gap junctions facilitate direct communication between adjacent cells, allowing the transfer of small molecules and ions, which is crucial for maintaining homeostasis and coordinating cellular responses to stress or injury. In the context of cancer, connexins have been shown to have both tumor suppressive and pro-tumorigenic roles, depending on their expression levels and context within the TME,[96,97]

**ii. Pannexins**

Pannexins form channels that allow for the exchange of ions and small molecules between cells and their extracellular environment. They are involved in various signaling processes within the TME, including the release of ATP, which can influence tumor cell behavior and interactions with immune cells.[98]

**iii. Tight Junctions**

Tight junctions are composed of proteins such as claudins and occludins that create a barrier to regulate permeability between cells. They play a key role in maintaining the integrity of epithelial layers within tumors, which is vital for controlling the microenvironment around tumor cells.[99]

**iv. Anchoring Junctions**

Anchoring junctions include structures such as adherent junctions, desmosomes, and focal adhesions, which connect cells to each other and to the extracellular matrix (ECM). These

junctions are crucial for maintaining tissue architecture and supporting cell signaling pathways that can influence tumor growth and metastasis. For example, cadherins, which are involved in adherent junctions, help maintain cell-cell adhesion and can affect cellular responses to growth factors.[100]

**v. Integrin**

Integrin are a type of anchoring junction that mediate cell-ECM interactions. They play a significant role in signaling pathways that regulate cell survival, proliferation, and migration within the TME. The interaction between integrin and ECM components can also influence tumor cell behavior, including invasion and metastasis.[101]

Among the various cell communication pathways, direct cell–cell communication, particularly the juxtacrine signaling pathway, plays a crucial role in mediating tumor–stromal interactions, which are essential for maintaining tissue architecture and function. Within juxtacrine signaling, connexins and pannexins are key mediators of intercellular communication. Agents that inhibit these cell junction proteins can disrupt tumor–stromal communication, thereby interfering with tumor progression and tissue homeostasis.[102,103,104,105,106]

## SOME OF NATURAL SOURCES WHICH BLOCK CELL JUNCTIONS

**i. Carbenoxolone**

Carbenoxolone, a synthetic compound derived from glycyrrhetinic acid found in licorice root, is known for its broad inhibitory effects on gap junction intercellular communication (GJIC). It functions by disrupting gap junctions and disorganizing connexin structures within gap junction plaques, ultimately impairing direct communication between cells. Studies involving human breast cancer cells (MCF-7) have shown that carbenoxolone can block calcium signaling, suggesting its impact on key cellular communication pathways. Moreover, glycyrrhetinic acid derivatives, including carbenoxolone, have also been observed to inhibit gap junction activity in gastrointestinal smooth muscle tissue, reinforcing its classification as a non-selective gap junction blocker.[107,108]

**ii. Oleamide**

Oleamide, a naturally occurring fatty acid amide derived from oleic acid, has been identified as an inhibitor of gap junction communication. It interferes with cellular processes like extravasation—the leakage of cells or fluid from blood vessels into nearby tissue. In studies

using pancreatic cancer models, oleamide served as a negative control, effectively blocking the spread of the fluorescent dye Lucifer Yellow. This demonstrates its strong ability to prevent direct cell-to-cell communication through gap junctions.[109,110]

## STEP 3: TME REMODULATION

Since cancer cell survival is highly influenced by the surrounding context and tissue architecture, effective treatment strategies must focus on remodeling the tumor microenvironment (TME). Altering the TME can disrupt the supportive signals and structural framework that enable tumor growth, resistance, and progression.

## TARGETED COMPONENTS TO ALTER TME

### 1. HIF (HYPOXIA INDUCIBLE FACTOR)

Hypoxia-inducible factors (HIFs) are released in response to the low-oxygen (hypoxic) conditions commonly found within tumors. To adapt and survive, HIFs trigger a metabolic shift aimed at conserving and maximize oxygen use. This shift leads to the Warburg effect, characterized by increased glycolysis even in the presence of oxygen, the creation of an acidic microenvironment, incomplete oxidative phosphorylation (OXPHOS), and the accumulation of metabolic intermediates such as glutamate, fumarate, and succinate.[111,33,112,113]

## SOME OF NATURAL SOURCES USED TO TARGET HIF

### i. Dictamnus dasycarpus

Dictamnine, a naturally occurring furanoquinoline alkaloid extracted from *Dictamnus dasycarpus*, has shown potential in targeting colorectal cancer. Research on HCT116 cells revealed that dictamnine lowers the expression of HIF-1α protein by interfering with key signaling pathways, including mTOR/p70S6K/eIF4E and MAPK. By disrupting these pathways and limiting HIF-1α production, dictamnine effectively hinders cancer cell growth, movement, and invasive behavior.[114]

### ii. Sophora flavescens

Matrine, a bioactive alkaloid derived from the roots of *Sophora flavescens*, has been explored for its therapeutic potential in colon cancer. It has been found to reduce both the mRNA and protein levels of HIF-1α, thereby suppressing its overall production. Additionally, matrine disrupts the Warburg effect—a metabolic hallmark of cancer—by decreasing glucose uptake

and lactate production. These combined actions contribute to the inhibition of colon cancer cell proliferation.[115]

### iii. Berberidaceae spp

**Berberine**, a tautomeric alkaloid found in members of the Berberidaceae family, has been studied in breast cancer, ovarian cancer, colorectal adenoma, and colorectal cancer. A clinical trial found berberine reduces colorectal cancer recurrence after polypectomy. Preclinical studies show it reverses therapeutic resistance, down modulates miR-93 to sensitize ovarian cancer cells to cisplatin, and down regulates ABC transporters (ABCB1, ABCC1) to improve doxorubicin effects on breast cancer *in vivo*. Berberine reduces HIF-1α and AMPK levels to alleviate hypoxia-mediated doxorubicin resistance in breast cancer and may sensitize cancer cells by regulating the AMPKα2-HIF-1α axis. It inhibits hypoxia-induced HIF-1α accumulation by promoting its lysine acetylation. Berberine suppresses HIF-1α protein production and suppresses mTOR signaling in colorectal cancer cells.[116]

### iv. Turmeric (**Curcuma longa**)

Source of curcumin, a polyphenol compound. Curcumin can decrease survival of liver and breast cancer cells. The role of HIFs is involved. Curcumin did not inhibit HIF-1α directly but inactivated HIF-1 by degrading ARNT and decreasing HIF-2α in breast cancer stem-like cells. It interferes with metastasis by indirectly targeting HIF-1α by degrading HIF-2α and. Turmeric is also a source of Calebin A, which partially hindered the migration of HCT-116 cells by suppressing HIF-1α. Calebin A suppresses HIF-1α activation and promotes apoptosis.[117]

### v. Ginseng (Panax spp.)

Ginsenoside Rg3, a bioactive compound derived from *Panax* species, has been shown to reduce epidermal growth factor (EGF)-induced expression of hypoxia-inducible factor 1-alpha (HIF-1α), thereby promoting apoptosis (programmed cell death) in liver cancer cells. In *in vivo* studies, it effectively suppressed tumor growth in hepatocellular carcinoma LM3 (HCCLM3) xenograft models. A clinical trial is currently underway investigating the therapeutic efficacy of Ginsenoside Rg3 in combination with standard chemotherapy for the treatment of advanced gastric cancer.[118] Another compound, panaxadiol, has demonstrated anti-tumor properties by inhibiting the expression of programmed death-ligand 1 (PD-L1) and reducing tumor cell proliferation. These effects are mediated through suppression of HIF-1α and signal transducer and activator of transcription 3 (STAT3) signaling pathways in

human colon cancer cells. Furthermore, panaxadiol has been shown to down regulate HIF-1α expression under hypoxic conditions via inhibition of the phosphoinositide 3-kinase/protein kinase B (PI3K/AKT) signaling pathway in colorectal cancer cells.[119]

## 2. ACIDIC ENVIRONMENT

The occurrence of the Warburg effect leads to the accumulation of lactic acid as an end product of aerobic glycolysis, resulting in an acidic tumor microenvironment. This acidic condition promotes tumor progression by supporting invasion, immune evasion, and resistance to therapy. To counteract this, there are two main approaches to reduce the acidity of the tumor microenvironment: neutralizing extracellular acidity and inhibiting lactate production via lactate dehydrogenase inhibition.

## AGENTS USED TO REDUCE ACIDITY

### I. Alkalizing agents

Several polyphenols have shown promise as anticancer agents, particularly in their ability to target pathways related to tumor growth and development. Some of these include curcumin, resveratrol, quercetin, epigallocatechin-3-gallate (EGCG), apigenin, kaempferol, and others. These polyphenols can act as alkalizing agents in tumor cells by influencing signaling pathways, potentially altering tumor cell behavior and reducing their aggressiveness.[120,121,122]

### II. Lactate dehydrogenase inhibitor

#### i. Myristica fragrans Houtt. (Nutmeg)

Water extracts from the seeds of Myristica fragrans have been demonstrated to inhibit the in vitro enzymatic activity of LDH. This inhibition led to a decrease in lactate production and overall metabolic activity in HT29 human colon cancer cells. Furthermore, these extracts effectively suppressed tumor growth in mice models, indicating their potential as an LDH inhibitor in cancer treatment.[123]

#### ii. Berberine

Berberine, a natural product, has been identified as a functional inhibitor of LDHA (a specific isoform of LDH). It reduced the activity and expression of LDHA in pancreatic adenocarcinoma (PAAD) cells, thereby inhibiting cell proliferation and invasion in both in vitro and in vivo studies. The findings suggest that berberine could serve as a therapeutic agent targeting LDHA in cancer.[124]

**iii. Gossypol**

Gossypol, a compound derived from the cotton plant, has been shown to inhibit various LDH isozymes in boar spermatozoa and goat tissues. It affects LDH activity in both the forward (pyruvate to lactate) and reverse (lactate to pyruvate) reactions, suggesting its role as an LDH inhibitor.[125]

## 3. ADIPOCYTE REMODULATION

Excess body fat leads to chronic inflammation, primarily driven by immune cells called adipose tissue macrophages (ATMs). Originally, fat cells (adipocytes) were thought to be passive storage for triglycerides, but they are now known to function as endocrine organs**,** releasing over 600 adipokines, including hormones and cytokines that regulate appetite, inflammation, insulin sensitivity, and more. As obesity progresses, fat cells enlarge, secrete more pro-inflammatory proteins like TNF-alpha and IL-6, and can outgrow their blood supply, leading to hypoxia and cell death. Macrophages from the immune system migrate to adipose tissue to clear these dead cells, increasing the number of ATMs—from 5% in lean individuals to 50% in obese ones**.** While ATMs clear dead fat cells, they also release inflammatory cytokines that contribute to chronic systemic inflammation**,** which can promote cancer**.** Type 2 diabetes etc., TNF-alpha further suppresses adiponectin, a beneficial adipokine that enhances insulin sensitivity and fat metabolism.[134,135,136]

Adipocytes can be remodeled by increasing the supply of adiponectin, which enhances the anti-inflammatory properties of adipose tissue and promotes fat-burning processes, contributing to a healthier metabolic environment.[126,127,128,129]

SOME OF THE NATURAL SOURCES OF ADIPONECTIN INDUCERS

**i. Mangifera indica L. leaf extract (MLE)**

MLE significantly enhances adiponectin levels and secretion in murine preadipocyte cells during differentiation, indicating its potential as a pharmacological candidate for the treatment of obesity and metabolic syndrome.[130]

**ii. Catechin**

Catechin has been identified as an activator of PPARγ, a key regulator of adipocyte function and metabolism. It has also been shown to increase circulating levels of high-molecular-weight (HMW) adiponectin, the biologically active form of the hormone, thereby supporting its potential role in improving insulin sensitivity and managing metabolic disorders.[131]

### iii. Genistein

Genistein is a plant-derived compound known to stimulate the adiponectin signaling pathway, contributing to improved metabolic health. It has also been studied for its potential role in cancer therapy, with higher dietary intake linked to a reduced risk of certain cancers, likely due to its anti-inflammatory, antioxidant, and hormone-modulating properties.[132]

### iv. Hesperetin

Hesperetin is a naturally occurring flavonoid that activates PPARα, a nuclear receptor involved in lipid metabolism and energy homeostasis. By modulating PPARα activity, hesperidin enhances adipocyte function, promoting improved lipid utilization and reducing inflammation, which may contribute to better metabolic balance and reduced risk of metabolic disorders.[132]

## SOME OF NATURAL SOURCES WHICH REDUCES FAT CONTENT IN BODY

### i. Quercetin

Quercetin has been reported to down regulate the expression of carnitine palmitoyltransferase 1 (CPT1), a key enzyme involved in the transport of fatty acids into mitochondria for β-oxidation, in a breast cancer cell model. This down regulation leads to a reduction in β-oxidation activity, suggesting that quercetin may inhibit, rather than enhance, fat burning through fatty acid oxidation (FAO). This highlights its complex role in cellular metabolism, particularly in the context of cancer.[133]

### ii. Arctigenin

Arctigenin has been shown to down regulate fatty acid oxidation by suppressing the expression of CPT1 in colonic macrophages, indicating its potential role in modulating immune cell metabolism within the tumor microenvironment. However, its direct impact on fatty acid oxidation in tumor cells remains unclear based on the current evidence, suggesting the need for further investigation to fully understand its role in cancer metabolism.[133]

### iii. Betulinic Acid

Betulinic acid, when delivered in a liposome-encapsulated form, has been shown to reduce cell proliferation and suppress the expression of key metabolic enzymes, including CPT1A, in colorectal cancer cells. Since CPT1A plays a crucial role in facilitating fatty acid oxidation (FAO) by enabling the transport of long-chain fatty acids into the mitochondria, its inhibition

by Betulinic acid suggests a targeted disruption of tumor energy metabolism through the suppression of FAO.[133]

## SUMMARY

Tumor cell survival and progression are dependent on the tumor microenvironment (TME), which facilitates malignant transformation, immune evasion, metabolic reprogramming and therapeutic resistance. While conventional chemotherapeutic strategies primarily target rapidly dividing tumor cells, they often neglect to focus on rate of cell proliferation. The therapeutic approach to altering the tumor microenvironment (TME) involves converting the pathological, maladaptive environment into a normalized, homeostatic state. Therapeutic strategies are orchestrated in a sequential manner to systematically reprogram the (TME). The first step involves restoring the pathological, stress-induced adaptive response to a normalized, homeostatic environment. In the second step, the objective is to disrupt the bidirectional communication between tumor cells and stromal components, as tumor cell survival and persistence heavily rely on these interactions. The third step focuses on remodeling the TME by targeting HIF, acidic environment, adipocyte remodulation. Where HIF offer metabolic shift and neoangiogenesis, acidic environment contributes to cell proliferation and metastasis and adipocyte fuels cancer progression by releasing cytokines. An emerging paradigm in TME modulation involves the use of phytochemicals derived from medicinal plants. Unlike synthetic agents, many plant-based compounds exhibit lower toxicity profiles and are more readily integrated into endogenous physiological pathways, making them particularly well-suited for long-term modulation of a chronically dysregulated microenvironment. Numerous plant-derived compounds including berberine, curcumin, quercetin, genistein, arctigenin, betulinic acid and ginsenosides have demonstrated TME-modulatory effects via diverse mechanisms. These include inhibition of stress hormone, fatty acid oxidation, down regulation of LDH activity, normalization of adipokine signaling (e.g., adiponectin), and suppression of HIF-1α expression. Collectively, a therapeutic strategy that integrates direct cytotoxic agents with TME-targeted phytochemicals holds considerable promise. The overarching therapeutic strategies is not merely to kill tumor cells, but to alter the pathophysiological state of the TME towards one that is unfavorable for cancer growth and maintenance. By concurrently attacking the tumor and its supportive microenvironment, this dual-modality approach may enhance treatment efficacy, improve patient tolerability and enable more durable disease control.

## CONCLUSION

This review shows that uncontrolled cell proliferation is one of the maladaptive branch to counteract stress. So instead of cutting the branches of cancer tree with radiation, chemotherapy and surgery which leads to strengthening the root of cancer tree and promotes faster development of new branches. A more effective strategy may lie in targeting the root cause by alleviating physiological stress and reprogramming the TME to restore a balanced, non-permissive environment for cancer progression.

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