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Review

2′-Hydroxyflavanone: A Bioactive Compound That Protects against Cancers

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Abstract: Cancer is defined as a multifactorial disease because it exhibits the continuous proliferation of malignant cells. It is one of the principal causes of death worldwide, with breast cancer occurrence being the highest among women and lung cancer being the highest among men. Hydroxyflavanones come under the category of flavonones and are further classified as 2′-hydroxyflavanone, 4′-hydroxyflavanone, 6-hydroxyflavanone, 7-hydroxyflavanone, etc. Flavonoids constitute approximately 60% of the total dietary polyphenols. Dietary components such as vegetables, fruits, cereals, soybeans, and tea are the chief sources of flavonoids, while citrus fruits contain a high amount of hydroxyflavanones. 2′-Hydroxyflavanone is known to have anti-inflammatory, antimutagenic, and anticancer activities. Hence, it is being investigated as a treatment for various diseases, especially cancer. 2′-Hydroxyflavanone can act as a chemotherapeutic agent in cancer. It restricts the signal transducer and activator of the transcription 3 pathway (STAT3) in some forms of cancer.

Keywords: hydroxyflavanone; cancer; anti-inflammatory; anti-cancer effect

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1. Introduction

In medical science, cancer is defined as a multifactorial disease because it exhibits continuous proliferation of malignant cells due to the deactivation of tumor suppressor genes, initiation of proto-oncogenes, and influential environmental factors. It is among the prime causes of death worldwide, with breast cancer occurrence being the highest among women and lung cancer being the highest among men [1]. Early diagnosis of cancer increases the effectiveness of chemotherapy and surgical treatment in cancer-affected individuals. Early eradication, recognition, and progression of cancer are among the vital roles played by the immune system [2]. Flavonoids constitute approximately 60% of the total dietary polyphenols [3]. Dietary components such as vegetables, fruits, cereals, soybeans, and tea are the chief sources of flavonoids, while citrus fruits contain a high amount of in 2′ hydroxyflavanone (2HF). Anthocyanins, flavonols, flavonones, flavones, isoflavones, and flavonols are the most commonly defined subclasses of flavonoids [4]. A diet including legumes, fruits, vegetables, grains, and beverages such as tea provide required bioactive compounds such as flavonoids, terpenoids, alkaloids, and glycosides [5]. Phytochemicals, minerals, fibers, and vitamins are supplied by a wide range of whole grains, fruits, and vegetables [6]. Flavonoids are compounds that affect the metabolism of the body through biological effects [7]. The subclasses of flavonoids are categorized based on the C-ring hydroxylation pattern, glycosylation or alkylation of the hydroxyl groups, oxidation of the C-rings, substitution at the third position, and attachment of the B ring to the carbon of the C-ring [8,9]. The basic structure of flavonoids consists of two benzene rings, a common diphenyl propane-flavone carbon skeleton, and a linear three-carbon chain [4,10]. The absorption of flavonoids is driven by the sugar residue attached to them

as β-glycosides [11]. Hydroxyflavanone comes under the category of flavonones and is further classified as 2′-hydroxyflavanone, 4′-hydroxyflavanone, 6-hydroxyflavanone, and 7-hydroxyflavanone (Figure 1).

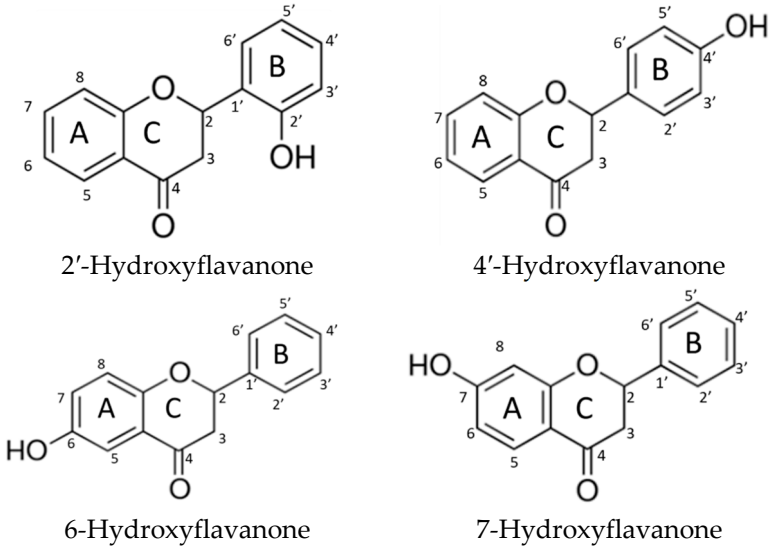

Figure 1. Chemical structure of hydroxyflavanone.

Various reports suggest that hydroxyflavanone possesses anti-oxidant, anticancer, anti-inflammatory, and antimutagenic properties. Antioxidant properties of the flavonoids make them good free radical scavengers, which helps in delaying certain diseases such as Alzheimer's and Parkinson's [12]. The anti-cancer activities of hydroxyflavanones, specifically 2′-hydroxyflavanone, include modulation of n numerous signaling pathways involved in apoptosis, angiogenesis, cell proliferation, and cell invasion. The depletion of the mesenchymal markers fibronectin and vimentin accompanied by a simultaneous increase in E-cadherin leads to the inhibition of epithelial–mesenchymal transition (EMT) [13].

2. Role of 2′-Hydroxyflavanone in Various Cancers

2.1. Renal Cancer

The kidney is the primary organ affected by renal cancer, mainly occurring as a neoplasm in the cortex of the kidney. Under normal conditions, the kidney helps in the purification of blood by eliminating waste products. When normal renal cells mutate and proliferate at a higher rate, they convert to carcinoma cells, which further form a tumor that results in the abnormal functioning of the kidney. The incidence of colorectal cancer is about 10% [14]. Generally, Von Hippel–Lindau (VHL) gene mutation is the leading cause of renal cell carcinoma (RCC). Renal cancer shows resistance to conventional radiotherapy and chemotherapy. In developed countries, the numbers of renal cancer cases are on the rise, and men seem to be more prone to RCC than women [15].

When there is a loss of VHL, the epidermal growth factor receptor (EGFR) is upregulated, leading to the progression of tumors due to its activation and upregulation of both Akt and P13K signaling pathways. In vitro studies show that the rise in the levels of epidermal growth factor due to VHL is inhibited by 2HF, leading to the abolishment of VHL-mutant RCC by inhibiting the Akt andP13K signaling pathway. Glutathione S-transferase pi (GSTπ) is expressed in high levels in VHL-mutant RCC. It is essential for cell adhesion and proliferation. 2HF is anti-cancerous as it inhibits angiogenesis and the activity of GSTπ in VHL-mutant RCC. The in vivo study using mouse xenografts supports the in vitro results, as when 2HF is administered orally to the mouse xenograft it can show anti-cancer effects in VHL-mutant RCC by inhibition of Akt signaling. 2HF reduces the levels of the proteins CDK4 and cyclin B1, which leads to a halt of the cell cycle at the G2/M phase [16–18]. Preclinical and mouse xenograft studies demonstrate that 2HF can

prohibit the development of VHL–mutant cancer and safeguard the VHL locus as it leads to caspase-mediated apoptosis in the colorectal cancer cells due to the decrease in the expression of anti-apoptotic Bcl-2 family protein and p21 upregulation. Hence, 2HF and its derivatives can be potential chemotherapeutic agents for RCC [19].

2.2. Breast Cancer

Breast cancer (BC) commonly occurs in women and rarely in men. BC occurs when there is an abnormal multiplication of cancerous cells forming a lump in the breast. The incidence of breast cancer (11.7%) has exceeded the incidence of lung cancer (11.4%) in women, making it the leading cause of death among women [14]. The detection of BC at early stages increases the chance of survival by 80%. Metastatic cancer can spread to nearby organs, such as the lungs, liver, and brain [20].

In MCF7 cells, 2HF intensified the inhibitory action of imatinib mesylate/gleevec and depleted the estrogen receptor (ERα). 2HF inhibits the TGF-β1 canonical pathway and switches on tumor suppressor 53 (TP53) in MCF7 and MDA-MB-231 cells. The level of the mercapturic acid pathway transporter 76kDaral-interacting protein (RLIP76) is elevated in BC as it is important in cancer cell growth and metastasis. It is a multifunctional protein as it is a transporter of glutathione electrophile conjugates (GS-Es), and takes part in mitotic spindle formation by binding to Ral, in response to stress it shifts between, the nucleus, cytosol, and membranes it is present throughout the cell. 2HF not only increases RLIP76 exhaustion in BC cells but also restricts the transport of doxorubicin in BC cells [21]. The efflux of doxorubicin is inhibited by 2HF, elevating its levels in the cell [13]. In vitro studies with MDA-MB-231 BC cells demonstrated a reduction in RLIP76 by 2HF. The cells lose their ability to move when 2HF inhibits angiogenesis in vivo and in vitro due to the depletion of CD31 and vascular endothelial growth factor (VEGF), respectively [16]. The expression of the receptor tyrosine-protein kinase erbB-2 (HER2) gene is downregulated by 2HF in SKBR3 cells [21]. 2HF also prohibits the switch on of the STAT3 pathway causing inhibition of cell proliferation [22] (Figure 2). Numerous biological processes are dependent on STAT3, a multipurpose transcription factor. Janus kinases (JAKs) activate STATs in the cytoplasm via transduction of cytokine-mediated signals. When the ligand binds to the receptor, JAK auto-phosphorylates, which further leads to the phosphorylation of STAT and its activation, forming a homodimer. It further moves into the nucleus and helps in the signal interchange between the nucleus and the cytoplasm. In this way, STAT3 helps in many biological processes such as cell proliferation, survival, and maturation of cells [23,24]. In the normal cells, the activation of STAT3 is strictly regulated, but when the activation continues beyond the required need it leads to tumorigenesis and involves migration, cell proliferation, invasion, and angiogenesis [25]. Thus, STAT3 is contemplated as oncogenes [23]. In breast cancer, Oncostatin M (OSM) causes the phosphorylation of STAT3 and an increase in interleukin-6 (IL-6), leading to its progression [24].

2HF possesses antimetastatic and antiproliferative activities. In comparison to a single treatment, no metastasis or decrease in tumor weight was observed when a breast-to-lung metastasis-based orthotopic mouse model was administered a combination of 2HF, RLIP antibody (Rab), and RLIP antisense (RAS). In vitro studies with triple-negative BC cell lines demonstrate a decrease in the expression of RLIP, KRAS, pP70S6K, pSTAT, and pERK by 2HF. RLIP76 inhibition leads to the loss of the invasive and migratory ability of BC cells [26].

2.3. Lung Cancer

Lung cancer is the most common type of cancer among men. The occurrence of lung cancer is higher in men than in women, but for the last couple of years, the incidence of lung cancer has also increased in women. Tobacco and smoking are the major causes of lung cancer in India and worldwide [27]. Lung cancer occurs due to tumor formation within the bronchi and the lung parenchyma [28].

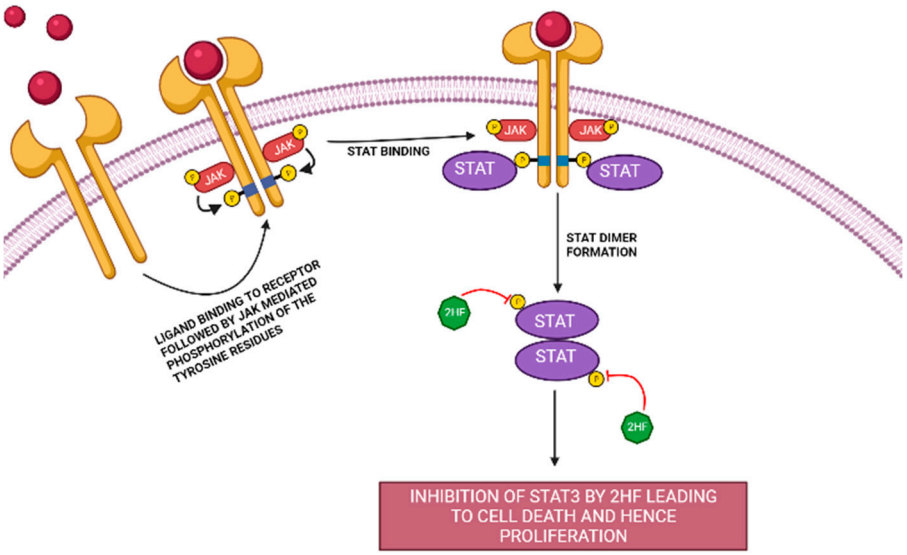

Figure 2. Upon binding of the ligand to the receptor, JAK phosphorylates the C-terminal end of STAT, and STAT forms an active dimer. 2′-Hydroxyflavanone inhibits the phosphorylation of STAT and leads to apoptosis of cancer cells) [22].

Apoptosis occurs in both types of histological lung cancers, i.e., small cell (SCLC) and non-small cell (NSCLC) upon treatment with 2HF. Cell proliferation and growth are inhibited as 2HF suppresses RPS6KB1 (P70S6K), PIK3CA, CCNB1, CDK4, and AKT signaling. The movement of doxorubicin out of the cell is inhibited by 2HF, resulting in its assemblage in the cells. A drop in the levels of the mesenchymal markers fibronectin and vimentin with a simultaneous increase in E-cadherin results in the inhibition of epithelial–mesenchymal transition (EMT). 2HF affinity chromatography illustrates the successful binding of RLIP to 2HF [13].

2HF prohibits the phosphorylation of p38 mitogen-activated protein kinase (MAPK) and extracellular signal-regulated kinase 1/2 (ERK1/2). The inactivation of the p38MAPK and ERK1/2 pathways due to 2HF led to a decline in the expression of matrix metalloproteinase (MMP-2) and urokinase-type plasminogen activator (u-PA) (Figure 3). A culture treated with SB203580 p38 (MAPK inhibitor) and U0126 (ERK 1/2 inhibitor) showed a decrease in the expression of MMP-2 and uPA along with inhibition of cell invasion. 2HF also weakens the activation of AP-1 and NF-kappa B. Oral administration of 2HF in vivo restricts the metastasis of A549 cells and Lewis lung carcinoma (LLC). Therefore, 2HF restricts the motility, invasion, and cell-matrix adhesion of A-549 cells [29]. Multiple cellular processes such as apoptosis, differentiation, proliferation, and stress response are mediated by MAPK cascades of signaling pathways. The prolonged activation of ERK is responsible for cancer and its progression, whereas a regulated expression is important for development. The pathway plays a critical role in the development and existence of tumor cells [30]. When the growth factors bind to the receptors on the cell surface, there is upregulation in Ras-guanosine triphosphate (GTP), which leads to the activation of the kinase. The GTP-bound Ras binds and leads to Raf kinase attachment to the plasma membrane. Further, it auto-phosphorylates or is phosphorylated by other kinases. Then there is sequential phosphorylation and activation of MEK followed by ERK1/2 [31]. The aberrant activation of the MAPK pathway leads to tumor formation.

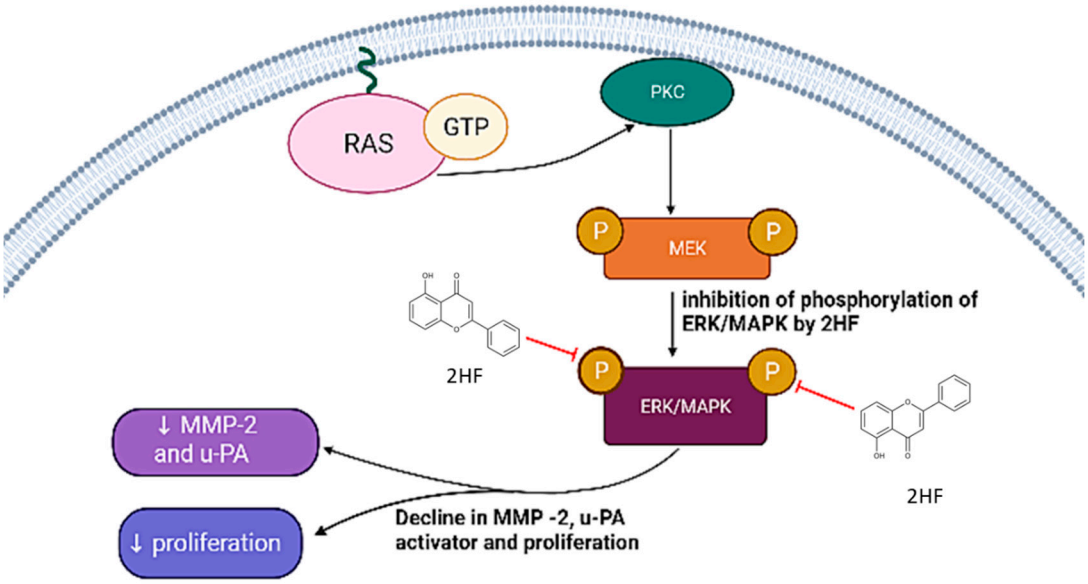

Figure 3. Inhibition of the MAPK pathway by 2′-Hydroxyflavanone [29].

2.4. Prostate Cancer

The mortality index in males seems to be increasing recently due to prostate cancer. According to recent statistics from the global cancer observatory, it has been confirmed that 1.4 million males have been affected by the disease across the globe [14]. Numerous studies reveal that men above the age of 65 years are at a higher risk of acquiring cancer.

2HF initiates apoptosis in DU145 and PC-3 cells, leading to inhibition of cell proliferation. It restricts the proliferation of LNCaP cells caused by androgen and attenuates androgen responsiveness by downregulating androgen receptive (AR) protein. Therefore, it also leads to the idea that the reoccurrence of prostate cancer can be obviated by this agent [32]. 2HF delays subcutaneous tumor growth in vivo and inhibits cell proliferation in prostate cancer (PCa) cell lines in vitro. 2HF also causes the repression of Akt phosphorylation, STAT3 phosphorylation, and transactivation, leading to cell apoptosis via caspase [33]. The prohibition of the STAT3 pathway caused by 2HF is also observed in pancreatic cancer cells [34]. 2HF displays antitumor effects in PCa cell lines in a dose-dependent fashion. It also leads to apoptosis via the Akt pathway and cell death by the unplanned or prolonged entry of cells into mitosis. As the dose of 2HF increases, the number of apoptotic cells also increases. 2HF decreases the expression of AR protein and PSA messenger RNA (mRNA), restricting the activity of AR protein [35]. 2HF causes the suppression of the Wnt/β-catenin signaling pathway by further abolition of β-catenin expression, GSK-3β phosphorylation, and transactivation, which leads to EMT inhibition, cell migration, and invasion [36]. The human prostate gland exhibits high levels of Aldo-keto reductase family 1 member C3 (AKR1C3) mRNA during prostate cancer. AKR1C3 governs the binding of the ligand to androgen. As 2HF inhibits AKR1C3, it can be targeted for developing agents that can treat hormone-dependent forms of cancer. Hence, 2HF could be utilized in treating prostate or breast cancer [37].

2.5. Osteosarcoma

Osteosarcoma is a bone malignancy that arises from primitive mesenchymal cells involved in bone formation. It is more prevalent in males than in females and is mostly seen in children between the ages of 10–14 [38].

2HF induces apoptosis in 143B cells, which was confirmed by a mitochondrial membrane potential assay and 4′-6-diamidino-2-phenylindole staining. When treated with 2HF, the exhibition of death receptor 5 (DR5) and tumor necrosis factor-related apoptosis-inducing ligand (TRAIL) was elevated. There was a decrease in the viability of 143B cells

when 2HF was administered. After treatment with 2HF, the flow cytometry analysis displayed an increase in the number of hypodiploid cells in the sub-G1 phase whereas the resulting DNA content decreased in the G0/G1 phase of 143 B cells. 2HF inhibits the tumor growth of 143B cells in-vitro. It decreases the expression of B-cell lymphoma/leukemia-2 (Bcl2) but upregulates the cleavage of poly (ADP-ribose) polymerase, cytochrome C and B-cell lymphoma-extra small (Bcl2-Xs) expression in 143 B cells. As the effect of 2HF on the extrinsic TRAIL and intrinsic mitochondrial-dependent pathways leads to apoptosis of 143B cells, it displays great potential as an anti-cancerous compound for osteosarcoma [39].

2.6. Melanoma

Malignant melanoma is the most lethal form of skin cancer. Melanoma is caused by uncontrolled melanocyte proliferation and is mostly cutaneous. The incidence of melanoma has been on the rise for the past few years. It occurs mostly in lower latitude regions and among the fair-skinned regions [40].

A study conducted on the murine cell lines B16-F0, B16-F10, and SK-MEL-24 showed that topical application of 2HF leads to the apoptosis of melanoma cells. All three cell lines displayed drops in the levels of phospho-PDGFR-β and tumor necrosis factor α (TNFα). The cell lines SK-MEL-24 and B16-F0 show apoptosis due to the reduction in the levels of PARP-1, caspase-9, and caspase-3. Various endocytosis-controlled cancer signals are prohibited because of the drop in the levels of the RLIP76 protein. In addition, 2HF also leads to a reduction in BCL2, phospho-AKT, ki6, 7, and survivin [17,18]. Reduction in the levels of mesenchymal markers fibronectin and vimentin with a concurrent rise in E-cadherin results in the inhibition of EMT (Figure 4) [13,17,18]. Studies conducted on PCa cell lines DU145 and PC-3 display inhibition of EMT in a similar pattern. As the dose of 2HF increases, there is a decrease in cell invasion and migration [16]. EMT takes place during embryonic development and other processes such as wound healing, tissue regeneration, and organ fibrosis but the same EMT also participates in metastatic invasion of tumor progression. It creates resistance in cancer treatment as it forms tumor cells with the properties of stem cells. Tumor and cancer cells display mixed mesenchymal and epithelial genes [41]. Mesenchymal cells have the surface markers N-cadherin, Vimentin, and Fibronectin, which are increased during EMT, whereas epithelial cells have E-cadherin on the cell surface, which decreases during the same [42]. The loss in the expression of E-cadherin and catenins is thought to be the reason for tumor relapse after therapy, local invasiveness, and dissemination into blood [43].

2.7. Gastric Carcinoma

One of the deadliest cancers in the world is stomach cancer. It affects the antral, cardial, or oxyntic mucosae [44]. Gastric cancer is categorized under stomach cancers. The incidence of stomach cancer was 1.09 million in 2020, with 769,000 deaths worldwide [29,45].

2HF inhibits the activation of the STAT3 pathway, leading to restricted cancer cell proliferation. It prohibits the proliferation of MGC-803 cells, exhibiting 88.9 ± 0.7%, 81.2 ± 0.5%, and 68.4 ± 0.5% declines in cell viability after treatment with 100, 200, and 400 µg/mL 2HF, respectively [22].

2.8. Bladder Cancer

Bladder cancer is ranked 10th among the most commonly occurring cancers among adults and there were 573,278 incidents in 2020 across the globe [29]. 2HF inhibits the proliferation of 5637, T24, UMUC-3, and 253J cells in a dose- and time-dependent manner. The protein expression of p-STAT3, MMP-9, p-AKT, and MMP-2 is diminished upon administration of 2HF. The ability of T24 cells to invade and migrate also decreases after 2HF treatment [46].

2.9. Colon Cancer

The 2020 occurrence of colorectal cancer worldwide was 1.9 million, with 935,000 deaths [11]. One major reason for the rise of colorectal cancer is improper diet. Cancer is on the rise in developed and developing countries due to the lifestyle habits of the people and the increasingly aging population [47]. The ability of HCT116 cells to replicate/duplicate themselves is inhibited by 2HF. Caspase activation and DNA fragmentation revealed that 2HF caused apoptosis in both wild-type and p53-null HCT116 cells. 2HF activates Egr-1, leading to increased expression of nonsteroidal anti-inflammatory drug-activated gene 1 (NAG-1). Apoptosis caused by 2HF can be inhibited using small-interfering RNA (siRNA) to cut off NAG-1 or Egr-1. The cell cycle inhibitor p21 and the proapoptotic gene are elevated by Egr-1 [48].

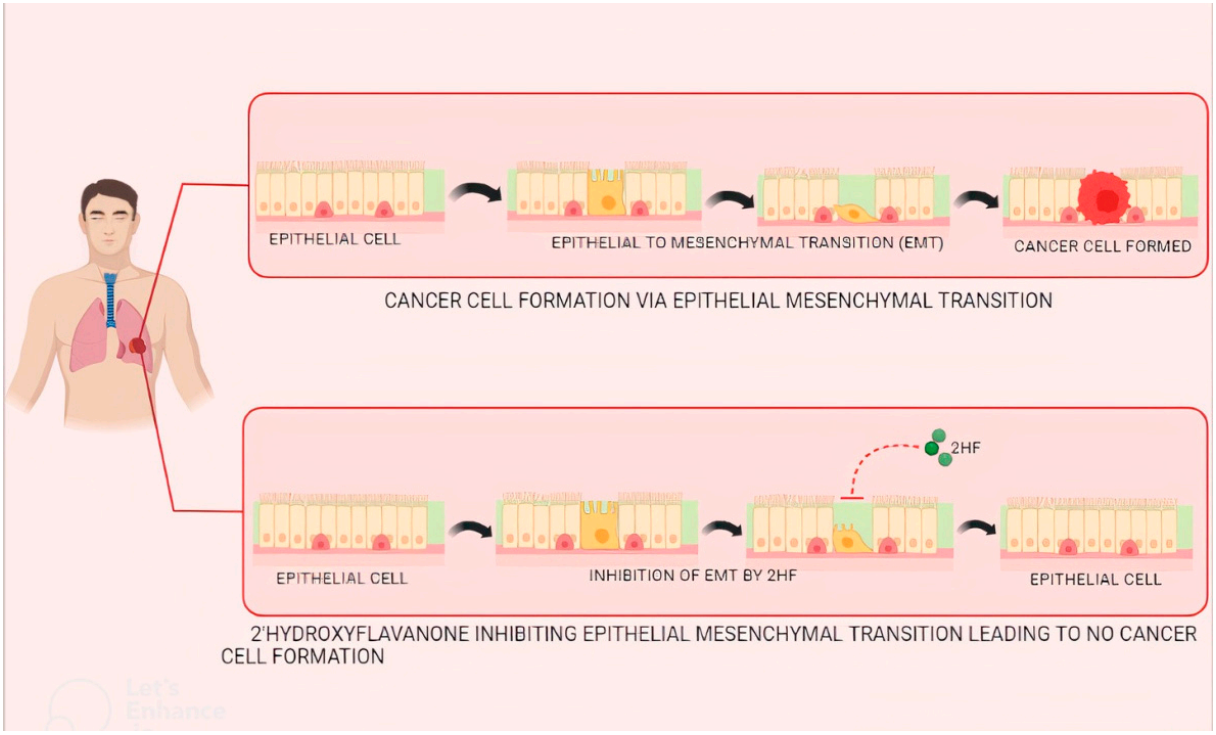

Figure 4. Inhibition of epithelial–mesenchymal transition by 2HF [13].

2.10. Pancreatic Cancer

Pancreatic cancer is an intractable type of cancer and its incidence is rising in developed countries. It mostly occurs in older individuals, wherein women are comparatively less affected than men [49]. The 2020 incidence of pancreatic cancer worldwide was 495,773, with 466,003 deaths [29].

2HF inhibits tumor growth, the STAT3 pathway, local invasion, and progression of pancreatic cancer cells by EMT, cell cycle arrest, and apoptosis. The movement and invasion of pancreatic cancer cells are restricted by 2HF in a dose-dependent manner. 2HF leads to an elevation in the levels of p27 (a cell cycle-inhibiting maker) and Bax (an apoptosis-promoting marker), a decrease in the levels of cyclin D1 and Bcl2 (an apoptosis-inhibiting marker), and an increase in the proportion of the cleavage subtype in poly-PARP and total-Caspase3, resulting in the apoptosis of cancer cells. Pancreatic cancer cells are arrested in the G1/G2 phase of the cell cycle upon treatment with 2HF [34].

The proliferation of HL-60 cells is inhibited by the 23 flavonoids, and their increasing concentrations enhance the effect. They show variation in the intensity of their effects. 3,6-Dihydroxyflavone was the strongest inhibitor, followed by luteolin, geraldo, 2HF, apigenin, 3,7-dihydroxyflavone, myricetin, fisetin, baicalein, quercetin, flavonone, chrysin, galangin, 4HF, 6HF, genistein, flavone, 7HF, daidzein, hesperetin, and naringenin in this

order. The enhanced effect of the inhibition by the flavonoids is attributed to the following: Ring B attached at position 2, ortho-substituting hydroxyls in ring B, and hydroxyls in position 3, 2, 3-double bond in ring C and appropriate hydroxyls [50]. Modulatory effects of 2-Hydroxyflavanone on the expression of certain genes and proteins involved in carcinogenesis (Table 1).

Table 1. Modulatory effects of 2-Hydroxyflavanone on the expression of certain genes and proteins involved in carcinogenesis.

Cancer Type	Inhibition by 2HF	Reduced Expression	Increased Expression	Ref.
Renal cancer	Epidermal growth factor	CDK4	-	[16]
Renal cancer	glutathione S-transferase pi	Cyclin B	-	[16]
Renal cancer	Angiogenesis	-	-	[16]
Renal cancer	VHL–mutant cancer	-	-	[16]
Breast Cancer	intensifies the inhibitory action of imatinib mesylate/Gleevec	estrogen receptor (ERα)	-	[21]
Breast Cancer	TGF-β1canonical pathway	expression of receptor tyrosine-protein kinase erbB-2 (HER2) gene	-	[21]
Breast Cancer	restricts the transport of doxorubicin in BC cells	-	-	[13]
Breast Cancer		RLIP, KRAS, pP70S6K, pSTAT and pERK. Invasive and migratory power of cells	-	[26]
Breast Cancer	RLIP76	CD31	-	[18]
Breast Cancer	Angiogenesis	vascular endothelial growth factor (VEGF)	-	[18]
Breast Cancer	Cell proliferation due to inhibition of switch on of the STAT3 pathway.	-	-	[22]
Lung cancer	RPS6KB1 (P70S6K), PIK3CA, CCNB1, CDK4, and AKT signaling	mesenchymal markers fibronectin and vimentin	E-cadherin	[13]
Lung cancer	Outflow of Doxorubicin	-	-	[13]
Lung cancer	epithelial-mesenchymal transition (EMT)	-		[13]
Lung cancer		Weakens the activation of AP-1 and NF-kappaB.	-	[29]
Lung cancer	phosphorylation of p38 mitogen-activated protein kinase (MAPK)	of matrix metalloproteinase(MMP-2)	-	[29]
Lung cancer	extracellular signal-regulated kinase 1/2 (ERK1/2)	urokinase-type plasminogen activator (u-PA)	-	[29]
Prostate cancer	Akt phosphorylation	-	-	[33]
Prostate cancer	-	androgen receptive (AR) protein	-	[32]
Prostate cancer	STAT3 phosphorylation		-	[34]

Table 1. *Cont.*

Cancer Type	Inhibition by 2HF	Reduced Expression	Increased Expression	Ref.
Prostate cancer		PSA messenger RNA	-	[35]
Prostate cancer	Wnt/β-catenin signaling pathway	β-catenin expression,	-	[36]
Prostate cancer	EMT	GSK-3β phosphorylation	-	[36]
Prostate cancer	Aldo-keto reductase family 1 member C3(AKR1C3)	-	-	[37]
Osteosarcoma	tumor growth of 143B cells in vivo	the amount of resulting DNA content	death receptor 5	[39]
Osteosarcoma	-	expressions of B-cell lymphoma/leukemia-2 in 143B cells	tumor necrosis factor-related apoptosis-inducing ligand	[39]
Osteosarcoma	-	-	the rise in the number of hypodiploid cells in the sub-G1 phase	[39]
Osteosarcoma	-	-	cleavage poly (ADP-ribose) polymerase, cytochrome C and B-cell lymphoma-extra small in 143 B cells	[39]
Melanoma	EMT	mesenchymal markers fibronectin and vimentin	E-cadherin	[13]
Melanoma	-	tumor necrosis factor α	-	[17,18]
Melanoma	-	levels of PARP-1, caspase-9, and caspase-3	-	[17]
Melanoma	-	RLIP76	-	[18]
Melanoma	-	BCL2, phospho-AKT, ki67, and survivin	-	[17,18]
Melanoma	-	phospho-PDGFR-β	-	[17]
Melanoma	-	in cell invasion and migration	-	[17,18]
Gastric Carcinoma	activation of the STAT3 pathway	cell viability	-	[22]
Gastric Carcinoma	cell proliferation of MGC-803	-	-	[22]
Bladder Cancer	-	p-STAT3, MMP-9, p-AKT and MMP-2	-	[46]
Bladder Cancer	-	Invasion and migration of T24 cells	-	[46]

Table 1. *Cont.*

Cancer Type	Inhibition by 2HF	Reduced Expression	Increased Expression	Ref.
Colon Cancer	HCT116 cells to clone itself	-	nonsteroidal anti-inflammatory drug-activated gene 1 due to activation of Egr-1	[48]
Pancreatic Cancer	Tumor growth	cyclin D1 and Bcl2 (an apoptosis inhibiting marker)	p27 (a cell cycle-inhibiting maker) and Bax (an apoptosis-promoting maker)	[34]
Pancreatic Cancer	STAT3 pathway	-	cleavage subtype in poly-PARP and total-Caspase3	[34]
Pancreatic Cancer	movement and invasion of the pancreatic cancer	-	-	[34]

3. Role of 2′-Hydroxyflavanone and Flavonoids in Diseases Other Than Cancers (Figure 5)

As the dose of 2HF increases, the proliferation of intracellular amastigotes and cellular promastigotes is inhibited in leishmaniasis. Cutaneous leishmaniasis due to both wild-type and antimony-resistant *Leishmania* species can be treated using leishmaniasis chemotherapy by 2HF. Oral administration of 2HF decreases the size of the lesion and the infection index in macrophages [51].

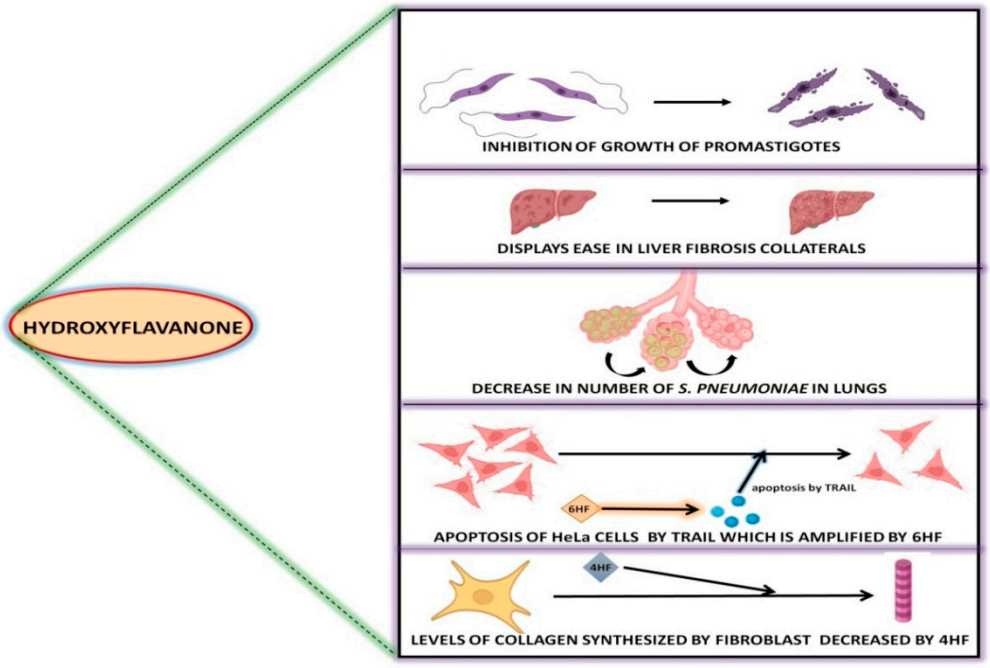

Figure 5. Hydroxyflavanone in diseases other than cancers [51].

In rats with early portal hypertension and liver fibrosis, no significant change is observed in the hemodynamics, but 2HF displays ease in the collaterals. This partially amplifies the apoptosis of mesenteric vascular endothelial cells [52].

Analysis of murine RAW 264.7 macrophages by flow cytometry revealed the prevention of LPS-induced macrophage apoptosis by 2HF. In murine macrophages, 2HF blocks LPS-induced loss of mitochondrial membrane potential, nitric oxide (NO) production, reactive oxygen species (ROS), and lipid peroxidation. Induction of the protein kinases SAPK/JNK and p38MAPK is forbidden by 2HF. LPS-induced phosphorylation, DNA binding of the redox transcription factor NF-kB, and nuclear translocation are also averted by 2HF. LPS-induced liberation of inflammatory chemokines and cytokines such as eotaxin, IL-12p40, IL-15, IL-2, MCP-1, LIX, IL-10, IL-17, and TNF-α is restricted by 2HF [53].

Docking studies were conducted between 11 hydroxyflavanones with hydroxy groups at various positions, one flavonone, and *Enterococcus faecalis* KAS III (efKAS III) disclosed the binding potential to efKAS III and the MIC values of these flavonones for E. faecalis and vancomycin-resistant E. faecalis (VREF). efKAS III docks well with naringenin, eriodictyol, and taxifolin due to their great binding affinities and high-scoring function. The major interactions for efKAS III inhibition are seen to be the side chain of Arg38, the 5′- and 4′-hydroxy group's hydrogen bonds among each other, and the backbone carbonyl of Phe308. Therefore, flavonones can be potential antimicrobials [54].

Generation of formyl-L-methionyl-L-leucyl-L-phenylalanine (fMLP)-induced superoxide anion by human neutrophils is inhibited by 2S-7′-hydroxyflavanone [55]. The number of viable *Streptococcus pneumoniae* in the lung decreased upon administration of 7′-hydroxyflavanone (1 mg/mouse) and *Zuccagnia punctata* extract (ZpE) (1 mg/mouse). The intake of Flavonoid 7HF extracted from *Zuccagnia punctata* or *Zuccagnia punctata* extract once or twice a day could be a potential treatment for respiratory infections [56]. An increase in the levels of P-glycoprotein (P-gp) expression was observed in HK-2 cells in the presence of ZpE or dihydroxyflavone (DHF) for 72 hrs, whereas the activity of HK-2 cells either dropped or remained unchanged. No effect of 7HF was observed in HK-2 cells [57]. Apoptosis induced by tumor necrosis factor-related apoptosis-inducing ligand (TRAIL) in HeLa cancer cells was amplified by 6-hydroxyflavanone (6-HF) and its derivative 6-propionoxy-flavonone (6-PF). A decrease in the mitochondrial membrane potential and an increase in the expression of the TRAIL-R2 death receptor led to the apoptosis of HeLa cells. Therefore, flavonones can be of potential use in TRAIL-based anticancer therapy, as they magnify the anticancer effects of TRAIL [58].

Collagen synthesis in human dermal fibroblasts by flavonone, flavone, and flavonol illustrate varying effects. There was a decline in the collagen concentration due to quercetin-3, 3′, 4′, 7-tetramethyl ether, flavonone, fisetin, and 4′-hydroxyflavanone. The levels of collagen increased with morin, rutin, and chrysin, with no change in the overall protein concentration. Naringenin displays no effect on total protein concentration or total collagen, whereas protein concentration drops due to the cytotoxicity of 5, 7-pentahydroxyflavone, quercetin-3,3,4′, 3-methyl quercetin, and 7-hydroxy flavone [59].

A comparison of the immunomodulatory activity of certain flavonoids between levamisole and cell-mediated immune responses and antigen-specific humoral and complement-mediated hemolysis demonstrated that the primary response in mice was inhibited by rutin, 6-hydroxyflavanone, and 7-hydroxyflavanone, while bavachinin amplified sheep erythrocyte (SRBC), 7′-methoxyflavanone, flavonone, and 6-methoxyflavonone-initiated both humoral immune responses-primary and secondary. There was the suppression of the secondary response and stimulation of the primary response in levamisole. No effect was seen on classical or alternative pathway-dependent hemolysis by any of the flavonoids. There was a decrease in the exhibition of SRBC-induced delayed-type hypersensitivity reactions by all the flavonoids. Therefore, flavonoids and their derivatives possess the immunostimulatory activity and are potential immunomodulators and immunosuppressants [60].

The exhibition of genes involved in cholesterol and fatty acid biosynthesis is controlled by the major transcription factor sterol regulatory element-binding proteins (SREBPs). De novo cholesterol and fatty acid synthesis are prohibited by 4HF. 4HF restricts lipid synthesis and SREBP maturation. The initiation of SREBPs and the expression of their target genes are decreased by 4HF in human hepatoma Huh-7 cells. 4HF also damages the activity of the fatty acid synthase promoter [61].

Urtica dioica, *Matricaria chamomilla*, and *Murraya koenigii* are plants that contain flavonoids such as quercetin, apigenin, myricetin, rutin, and kaempferol and have the potential to be used as a treatment or as a preventive measure against diseases related to stress and aging [62,63].

4. 2′-Hydroxyflavanone in Cellular Signaling

2′-Hydroxyflavanone plays a great role in the protection against diseases and various forms of cancer. It is abundant in fruits, vegetables, cereals, and tea. 2HF displays great potential as an anti-cancerous and anti-mutagenic compound. 2HF seems to be naturally available and safe as it is mostly present in dietary compounds. The bioactive compound not only regulates certain proteins such as ERα, HER2, 11β-HSD1, and AKR1C3, but also targets the transporter protein RLIP in breast cancer [64]. 2HF and its derivatives can be considered highly promising chemopreventive agents for RCC (15). It also interacts with the p38 (MAPK) and ERK1/2 pathways, leading to the inhibition of lung metastasis and RLIP to cause apoptosis [22]. The Wnt/β-catenin signaling pathway was suppressed by 2HF in prostate cancer [28]. 2HF affects the extrinsic TRAIL and intrinsic mitochondrial-dependent pathways, leading to apoptosis of 143B cells in osteosarcoma [31]. In most types of cancers, 2HF causes a decline in PARP-1, caspase-9, caspase-3, BCL2, phospho-AKT, ki67, survivin, p-STAT3, MMP-9, MMP-2, and cyclin D1. A rise in E-cadherin expression accompanied by a decrease in the mesenchymal markers fibronectin and vimentin led to the inhibition of EMT [20].

5. Conclusions

2′-Hydroxyflavanone helps inhibit cell proliferation and various pathways that aid in the progression of cancer. It interacts with various pathways including STAT3, MAPK, and Wnt/β-catenin to cause apoptosis or inhibition of proliferating cancer cells. The anti-cancerous activity of 2HF leads to a decrease in tumor size, inhibition of cancer, and its metastasis. Since cancer is a multifactorial disease, 2HF acts at various levels to control the progression of cancer by suppressing oncogenes and their respective proteins and expressing tumor suppressor genes and their respective proteins. 2HF is a bioactive compound that has great potential to be a plant-based drug since it is readily available from food sources such as citrus fruits such as oranges. Therefore, according to our review, more studies focusing on in vivo models could help develop the compound as a chemotherapeutic or a preventive drug for various forms of cancer.

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