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Pharmacological basis and new insights of taxifolin: A comprehensive review

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ABSTRACT

The pharmacological characteristics of phytochemicals have prompted a lot of interest in their application in disease management. Due to the high incidence of cancer related mortality and morbidity throughout the world; experiments have concentrated on identifying the anticancer potential of natural substances. Many phytochemicals such as flavonoids and their derivatives produced from food offer a variety of new anti-cancer agents which prevent the cancer progression. Taxifolin, a unique bioactive flavonoid, is a dietary component that has grabbed the interest of dietitians and medicinal chemists due to its wide range of health benefits. It is a powerful antioxidant with a well-documented effect in the prevention of several malignancies in humans. Taxifolin has shown promising inhibitory activity against inflammation, malignancies, microbial infection, oxidative stress, cardiovascular disease, and liver disease. Anti-cancer activity has been shown to be relatively significant than other activities investigated in vitro and in vivo with a little or no side effects to the normal healthy cells. In summary this review offers the synopsis of recent breakthroughs in the use of taxifolin as a cancer treatment, as well as mechanisms of action. However, to develop a medicine for human usage, more study on pharmacokinetic profile, profound molecular mechanisms, and drug safety criteria should be conducted utilizing well-designed randomized clinical trials.

1. Introduction

The consumption of fruits and vegetables is associated with a plenty of health benefits, encouraging scientists to investigate the presence of numerous bioactive compounds and their impact on human health [1]. The bioactive compounds, derived from plants, have been identified as novel agents, which showed a pivotal role in the inhibition and/or alleviation of different human ailments such as cancer, inflammation, cardiovascular disease, and neurodegenerative disease over the last few decades [2]. Among these bioactive compounds flavonoids have been identified to be most beneficial in terms of alleviation of human health. Flavonoids are nothing but the hydroxylated phenolic compound which comprises a benzo-γ-pyrone ring in its structure [3].

According to the various researches a wide range of pharmacological activities of flavonoids has been identified that includes antioxidant, anti-inflammatory, hepatoprotective, antiangiogenic properties [4], anti-diabetic [5], cardioprotective [6], neuroprotective, anti--Alzheimer's disease [7] which is mainly due to their degree of hydroxylation, structural class, other substitutions and conjugations, and degree of polymerization along with metal chelation activity [8]. Recent studies indicate that higher flavonoid intake in the diet is inversely related to mortality threat [9] and certain types of depression [9,10]. Natural product is also an important resource for anticancer drugs [1,4]. The natural bioactive compounds, especially the flavonoids have a significant impact on the treatment of carcinoma. They exhibit a strong antioxidant activity and neutralize the effects of free radicals due to the presence of hydroxyl groups, and they chelate metal ions [11].

Taxifolin, a flavonoid, has gained the attention for its large pharmacological actions [12,13] (Table 1) along with anticancer activities (Table 2) such as the prevention of angiogenesis, cytochrome P450 enzymes, P-glycoprotein, reactive oxidative species (ROS), and cell cycle regulators, as well as triggering of apoptosis [4].

Through the assessment of all the findings we plan to discuss various pharmacological and anticancer efficacy of taxifolin, as a naturally produced substance, via acting on various transduction pathways in this current review.

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Table 1
Pharmacological activities of taxifolin.

Activity/disease	*In vivo/ in vitro*	Animal model/cell line	Mechanism of action/outcome	Ref.
Antioxidant	*In vivo*	Wistar rats	Antioxidant activity along with the capillary protector action.	[38]
	In vivo	Wistar rats	Antioxidant effect.	[39]
	In vivo	Wistar rats	Decrease in the lipid peroxidation in liver and serum by reacting with the thiobarbituric acid.	[40]
	In vivo	Wistar rats	Inhibits the oxidative neuronal injuries in cortical cells and inhibition of lipid peroxidation.	[41]
	In vitro	human RPE (ARPE-19) cells	Inhibits the H_2O_2-induced poly (ADP-ribose) polymerase cleavage through translocation of Nrf2 to the nucleus and the activation of mRNA and protein expression	[43]
Anti-inflammatory	*In vivo*	Wistar rats	Regulate the activation of NF-κB, inhibits of the infiltration of leukocyte and the expression of COX-2 and iNOS in brain and prevented the expressions of Mac-1 and ICAM-1.	[44]
	In vivo and *In vitro*	C57BL/6 mice and RAW264.7, a murine monocytic cell line	Suppress the NF-κB activation, protein kinase activation by C-Fos and mitogen, and reduce the expression of osteoclast-specific genes, including Trap, Cathepsin K, Mmp-9, Nfatc1, C-Fos, and Rank. Repress the osteoclast activity by improving the ovariectomized-induced bone loss and decrease the levels of interleukin-6, interleukin-1β, necrosis factor-α, and RANKL in serum.	[45]
	In vivo and *In vitro*	RAW264.7 cells and C57/BL6 mice	Suppress RANKL-induced gene expression, tartrate-resistant acid phosphatase, matrix metalloproteinase-9 nuclear factor of activated T cells 1 and cathepsin K, and F-actin ring formation.	[46]
	In vitro	rat basophilic leukemia (RBL)-2H3 cells and human mast cell line	Inhibits the degranulation, generation of leukotriene C4 (LTC4), production of interlukin-6 (IL-6), and expression of cyclooxygenase-2 (COX-2) in bone marrow-derived mast cells and inhibition of RBL-2H3 and HMC-1 cells activation through Akt/IKK/NF-κB and MAPKs/cPLA2 signal pathway.	[47]
	In vitro	BV2 cell line	Protective mechanism against the CPF-induced BV2 cell toxicity through the upregulation of pAMPK level along with the activation of Nrf2/HO-1 signaling pathway.	[48]
Hepatoprotective	*In vitro*	Huh7 human hepatoma cells	Block the JFH-1 virus-induced oxidative stress.	[51]
	In vitro	HepG2 cells	Prevent concanavalin A induced hepatic injury in mice and also inhibits the TNF-α/ActD induced apoptosis through the regulation of caspase and NF-κB pathways.	[52]
	In vivo	C57BL/6 mice	Hepatoprotective activity against acetaminophen induced liver injury through downregulation of TNF-α, IL-6, Bax and increased mRNA expression of Nrf2, SOD2, Bcl-2 and procaspase-3.	[53]
Anti-Alzheimer	*In vitro*	N2a Swe cells	Attenuation of increased Aβ and C99 levels and inhibition of the amyloidogenesis via the downregulation of P-JAK2/P-STAT3-coupled NF-κB linked BACE1 expression through the upregulation of SIRT1.	[55]
	In vivo	Tg-SwDI mice	Blocks the formation of amyloid-β oligomer, restoring the vascular integrity and memory.	[56]
	In vivo	Tg-SwDI mice	Increases cerebral blood flow and removes amyloid-β from the brain and inhibits the cognitive dysfunction through the suppression of ApoE–ERK1/2–amyloid-β precursor protein axis.	[57]
	In vitro and *In vivo*	HT22 cell, BV-2 microglia cells and Swiss mice	Neuroprotective effect against oxytosis, ferroptosis and ATP depletion and reduction of the LPS-induced neuroinflammation.	[58]
Antiangiogenic	*In vitro*	Human Umbelical Vain Endothelial Cells (HUVECs)	Antiangiogenic activity through the inhibition of the formation of new blood vessels and branches.	[61]
Antihyperglycemic	*In vivo*	Albino rats	Inhibitory activity against α-amylase and the regulation of the postprandial hyperglycemia along with the anti-inflammatory and antioxidant activity.	[62]
	In vivo	Sprague–Dawley (SD) rats	Inhibitory effect against α-glucosidase, α-amylase and pancreatic lipase.	[63]
Glucose homeostasis	*In vivo* and *In vitro*	Spontaneously hypertensive (SHR) rats, Wistar-Kyoto (WKY) rats and Rat kidney tubular ductal epithelial cell line NRK-52E	Increase the protein levels associated with downstream glucose metabolism pathway of PI3K/AKT and maintain the glucose homeostasis with inhibition of RAAS and inflammatory responses.	[64]
Diabetic retinopathy	*In vivo*	Albino Wistar rats	Suppressed reactive oxygen species, IL-1b and TNF-a production.	[65]
Anticataractogenesis	*In vivo*	Wistar rats	Reduce status of oxidative stress and causes inhibition of p38 MAPK, ERK 1/2 and aldose reductase levels.	[66]
Cardiovascular	*In vivo*	Wistar-strain rats	Maintains the normal lipid profile in the serum and liver, and lipid excretion in fecal.	[67]
	In vitro	HepG2 cells	Inhibits of the cholesterol synthesis along with the reduction of the HMG-CoA reductase activity and suppression of the cellular cholesterol esterification, and triacylglycerol and phospholipid syntheses, decrease the hepatic lipid synthesis via decreasing and increasing the secretion of apoB and apoA-I.	[69]
	In vitro and *ex vivo*	BDIX rat embryonic heart tissue-derived H9c2 cells and Sprague–Dawley (SD) rats	Inhibit the oxidative stress and endoplasmic reticulum stress induced apoptosis via the PI3K/Akt pathway and delay of the onset of endoplasmic reticulum stress by regulating certain protein expression levels.	[70]
		Sprague–Dawley (SD) rats		[71]

(*continued on next page*)

2. Taxifolin: an overview of chemistry, sources, pharmacokinetic and toxicological perspectives

2.1. Sources

Flavonoids are the most abundant secondary metabolite found in plants (Fig. 1) with significant health-promoting effects [14–17].

It is estimated that the dietary intake of flavonoids to be 50 and 800 mg per day [18,19]. Taxifolin is 3,5,7,3′,4′-pentahydroxyflavanone or dihydroquercetin, which is a class of polyphenols. It is abundantly found in olive oil, grapes, in citrus fruits and onions [7]. Along with that it is also found in conifers like the Siberian larch, *Larix sibirica*, in *Pinus roxburghii*, in *Cedrus deodara* [20] and in the Chinese yew, *Taxus chinensis* var. *mairei* [21]. It is also obtain from the silymarin extract from the milk thistle seeds and in vinegars aged in cherry wood [22].

2.2. Structural chemistry

Taxifolin is a subclass of flavanonols, an isoflavanone in flavonoids family. The basic structure of the taxifolin (Fig. 2) consists of two phenyl groups (ring A and ring B) which are joined together by a heterocyclic ring referred to as ring C [23,24].

The structure contains 3-hydroxyl group at the C ring which is connected to the B ring at carbon-2 [24]. It is a pentahydroxyflavone containing five hydroxyl groups at the 3-, 3'-, 4'-, 5- and 7-positions. The IUPAC name of taxifolin is (2*R*, 3*R*)-2-(3,4-dihydroxyphenyl)-3,5,7-trihydroxy-2,3-dihydrochromen-4-one. It has (2R, 3R)-configuration and it is a conjugate acid of a (+)-taxifolin (1-), an enantiomer of a (-)-taxifolin. The molecular weight of taxifolin is 304.25 g/mol with the molecular formula $C_{15}H_{12}O_7$ [25]. Taxifolin has two stereocenters on the C-ring and it has 4 stereoisomers. Taxifolin with the configuration of (2R, 3R) is one of them and it comprises 2 pairs of enantiomers [26].

2.2.1. Structure-activity relationship

Taxifolin consist of two aromatic rings which comprise two phenolics groups (—OH) at the *meta*- and *para*-position with respect to each other. This phenolics group corresponds to its strong antioxidant activity [27]. The antioxidant activity of a molecule increases with increase in the number of hydroxyl groups attached to the aromatic ring [28]. The strong antioxidant activity of taxifolin mainly responsible for its conjugation structures and resonance stability of both phenolic rings [29]. The presence of C2-C3 double bond is very crucial for the inhibitory activity of flavonoids. Taxifolin lacks the C2-C3 double bond, which makes it very susceptible to inactivation through the formation of strong hydrogen bonds with the macromolecules. The presence of 3-OH group in the C ring responsible for the modulatory effect against neutrophils' oxidative burst. In the B ring the ortho arrangement of the catechol group is vital for the modulatory effect of flavonoids against neutrophils' oxidative burst [30]. The presence of catechol group is also very important for the inhibitory effect of taxifolin on the self assembly of Amyloid β-protein. It was reported that oxidation of the catechol moiety to o-quinone is responsible for the inhibitory effect of taxifolin, which causes formation of covalent conjugates with susceptible side chains in Aβ and leads to inhibition of Aβ assembly. The 3′- and 4′-hydroxyl groups of taxifolin is crucial for the inhibition of Aβ aggregation but the 7-hydroxyl group and the stereochemistry at positions 2 and 3 are not [31].

2.3. Pharmacokinetics perspectives

Several studies have been reported to have great differences in the taxifolin bioavailability when administered orally in rat. According to the experiment performed by Wang and his co researchers the plasma concentration was found to be very less after oral administration of taxifolin at a dose of 10–100 mg/kg body weight [32]. The bioavailability was evaluated 0.17% when compared to the intravenous administration. In another study, the treatment of the male rats with taxifolin at a dose level of 12.5, 25 or 50 mg/kg through single oral administration or 50 mg/kg by intravenous administration and the highest concentration of taxifolin was detected in blood plasma, kidney, liver, heart, spleen, brain, skeletal muscles, lungs for up to 24 h after administration. Along with that the maximum concentration of taxifolin in blood plasma was detected after 30 min of oral administration of the drug, which was absorbed quickly from the gastrointestinal tract (GI) and the levels were undetected after 8 h. In this research the bioavailability of taxifolin was found to be 24% as compared to the intravenous administration [33]. In rabbit, the bioavailability of taxifolin was found to be 36% after the introduction of the same at a dose of 8–80 mg/kg [34]. It was further reported that the taxifolin in converted to 3′- or 4′-O-methyl taxifolin in rats [35]. Another experiment was also conducted in two human volunteers. They consumed 2 g of taxifolin and the result obtained shows that taxifolin was converted into hydroxyphenylacetic acid, which was identical metabolite excreted following quercetin ingestion [36]. In summary, it showed the rapid absorption of taxifolin from the GI tract of rat and its distribution to the blood plasma, liver, heart, spleen, brain, skeletal muscles, lungs and kidneys, which is then metabolized and excreted via urine. The amount of pure taxifolin eliminated through urine is quite less.

Table 1 (*continued*)

Activity/disease	*In vivo/ in vitro*	Animal model/cell line	Mechanism of action/outcome	Ref.
	ex vivo and *In vivo*		Improved the ventricular functional recovery, the levels of SOD, GSH-PX and upregulation of antiapoptotic proteins such as Bcl2 and downregulation of proapoptoic proteins (Bax, Cyt-c, caspase 3 and 9), inhibition of apoptosis.	
Antimicrobial	*In vitro* and *in silico*	*Escherichia coli* VL-613, *Staphylococcus epidermidis* ATCC 14990, *Pseudomonas aeruginosa* 98, *M. luteus* ATCC 10240, *Micrococcus luteus (lysodeicticus)* ATCC 4698	Interaction with active amino acids of Mtb DNA gyrase and isoleucyl-tRNA synthetase.	[73–75]
Anti-psoriatic	*In vitro* and *In vivo*	Human immortal keratinocytes (Hacat) cell line and BALB/C mice	Inhibits the LPS-induced abnormal proliferation and regulates the T_h cells differentiation through the inhibition of several transcription factors such as T-bet, GATA-3 and RORγt, inhibition of Notch1 and Jak2/Stat3 signal pathways.	[77]
Anti-hyperuricemic	*In vitro* and *In vivo*	AML12 cells and ICR mice	Suppress the uric acid level in serum and liver and also suppress the hepatic xanthine oxidase activity.	[78]
Pulmonary	*In vivo*	Albino Wistar rats	Inhibits cisplatin-induced pulmonary toxicity.	[79]
Genotoxic	*In vivo*	C57Bl/6 mice	Prevents DNA damage and chromosome aberrations. Antifibrotic effect.	[80]
Antiviral	*In silico*	–	Inhibitor of Main Protease (Mpro) of SARS-CoV-2	[81,82]
Antifungal	*In vitro*	*Alternaria alternata, Aspergillus fumigatus, Aspergillus niger, Macrophomina phaseolina and Penicillium citrii*	–	[83]

2.4. Toxicological evaluation

Toxicity study for the taxifolin has been conducted by several researchers and the optimum dose has been derived for animals and as well as for the humans. The toxicity study has been performed prior to the determination of the toxic dose which was considered for being used as a food supplement in various marketed products. It was challenging to get a precise NOAEL (No Observed Adverse Effect Level) for taxifolin from larch wood as large concentrations of taxifolin did not elicit any adverse responses. Thus, a NOAEL of > 1500 mg/kg body mass could be defined for animals (e.g. a 6-month oral toxicity study in rats). The acceptable daily intake (ADI) is usually calculated from the NOAEL. The ADI is usually given in mg/kg body weight per day. Assuming a factor of 100, the taxifolin ADI for humans should be 15 mg/kg body mass (1050 mg/day for a 70 kg adult). However, additional health benefits with daily intakes higher than 1.5 mg/kg body mass (100 mg/day for a 70 kg adult) are not expected, therefore excessive taxifolin consumption would be of no benefit [37].

3. Taxifolin and its pharmacological activities

3.1. Antioxidant activity

Taxifolin is associated with antioxidant activity and capillary protecting action [38]. Additionally, it has also been found that the effectiveness of taxifolin is 3.4 times greater than quercetin at the dose of 100 mg/kg and 4.9 times for the dose of 300 mg/kg. It is also shown that taxifolin has antioxidant activity in vivo, which was evaluated in Wistar rats, suffering from tetrachloromethane induced hepatitis [39]. In another study, the rats treated with taxifolin show a decrease in the lipid peroxidation in liver and serum by reacting with the thiobarbituric acid, which reveals the antioxidant property of taxifolin [40]. The antioxidant activity of taxifolin is also exhibited through its neuroprotective effects via the inhibition of oxidative neuronal injuries in rat cortical cells, which was supported by the DPPH radical scavenging activity and the inhibition of lipid peroxidation [41]. The antioxidant potential of taxifolin was also evaluated by the deoxyribose degradation assay for its electrochemical redox potentials [42]. Taxifolin inhibits the

Table 2
Chemotherapeutic activities of taxifolin.

Cancer model	*In vivo/ in vitro*	Cell line/animal model	Dose	Mechanism of action/outcome	Ref.
Breast	*In vivo*	Sprague–Dawley (SD) rats	10, 20 and 40 mg/kg i.p.	Altered metabolism through interacting with the LXRs, HMG-CoAR and inhibits the uncontrolled cell proliferation.	[92]
	In vitro and *In vivo*	Human breast cancer cell line MDA-MB-231, Balb/c mouse mammary cancer cell line 4 T1 and Balb/c mouse	100 mg/kg orally for mice and 10, 30, 100 μM for cells	Inhibits the cancer cell proliferation, migration, prevents the EMT process, decreases the expression of mesenchymal markers and promotes MET and decreases the protein and mRNA expressions of β-catenin. Inhibits the growth of primary tumors and prevents the lung metastasis.	[98]
		Sprague–Dawley rats	10, 20, and 40 mg/kg i.p.	Downregulation of the expression of CYP1A1 and CYP1B1 via inhibiting AhR signaling pathway.	[109]
Lung	*In vitro* and *In vivo*	A549 and H1975 cells, and A549 xenograft BALB/c mice	1 mg/kg for mice and 0, 25, 50, 100 μM for cells	Inhibition of stemness by downregulating the protein expression of SOX2 and OCT4, and reduced CD133-positive cells. Reduce the invasiveness of the cancer stem cells and the expression of N-cadherin and vimentin with increased expression of E-cadherin and inhibited PI3K, TCF4 protein phosphorylation.	[121]
Colorectal	*In vitro* and *In vivo*	HCT116, HT29 cells and Athymic male mice	15, 25 mg/kg i.p. for mice and 40, 60 μM for cells	Arrest in cellular growth, alteration of the molecules which regulate the G2 phase of the cell cycle, and induced apoptosis. Decrease the expression of β-catenin, AKT and Survivin genes and protein expression.	[120]
Liver	*In vitro*	Hep G2 cells	1 μM	Expression miR-153, miR-204, miR-211, and miR-377-3p was downregulated, upregulation of the ZEB2 protein expression and inhibits Akt phosphorylation and thus diminishing ZEB2 signaling which in turn triggers the carcinogenesis.	[137]
Prostate	*In vitro*	Human androgen-independent prostate carcinoma cells DU145, immortalized human prostate cells PNT2, and normal human foreskin fibroblasts Hs27	IC50 500 mM	Antiproliferative effect by enhanced mitotic arrest and apoptosis through the cleavage of poly (ADP-ribose) polymerase, and caspases-7 and -9 and increased the microtubule polymerization, induce the formation of twisted and elongated spindles in the cancer cells and diminution of MAD2, improve the mitotic block, causing the activation of SAC which leads to the mitotic arrest.	[139]
	In vitro	Immature male Sprague–Dawley rats and Human testes	IC50 100 μM	Decrease basal, LH-stimulated, 8BR-stimulated, pregnenolone-mediated, and progesterone-mediated androgen production by Leydig cells and inhibited 3β-hydroxysteroid dehydrogenase and 17α-hydroxylase/17, 20-lyase enzyme activities.	[143]
Bone	*In vitro* and *In vivo*	Human osteosarcoma cell lines, U2OS and Saos-2 and BALB/c nude mice	25 mg/kg i.p. for mice and 0, 5, 10, 25 and 50 μM for cells	Promote the G1 cell cycle arrest and induction of apoptosis, downregulation of the expression of AKT serine/threonine kinase 1 (AKT), phosphorylated (p-Ser473) AKT, v-myc avian myelocytomatosis viral oncogene homolog (c-myc) and S-phase kinase associated protein 2 (SKP-2)	[148]
Skin	*In vitro* and *In vivo*	JB6 P+ mouse epidermal cell line and SKH-1 hairless mice	1mgtopically for mice and 0, 20, 40, 80 μM for cells	Suppression of the UVB-induced activation of EGFR and Akt and prevented downstream signaling cascade, attenuate the expression of COX-2 and prostaglandin E2 (PGE2) and inhibit the cellular transformation induced by EGFR. Suppress tumor incidence, volume and multiplicity.	[158]
	In vitro	SSCC cell line and the non-cancer skin cell line BJ-5TA	IC50 20 μM and 110 μM respectively	Inhibit the development of SSCC through apoptosis and cell cycle arrest and suppress the invasion of SSCC through the downregulation of matrix metalloproteinases (MMP) MMP-2 and MMP-9 expression.	[119]

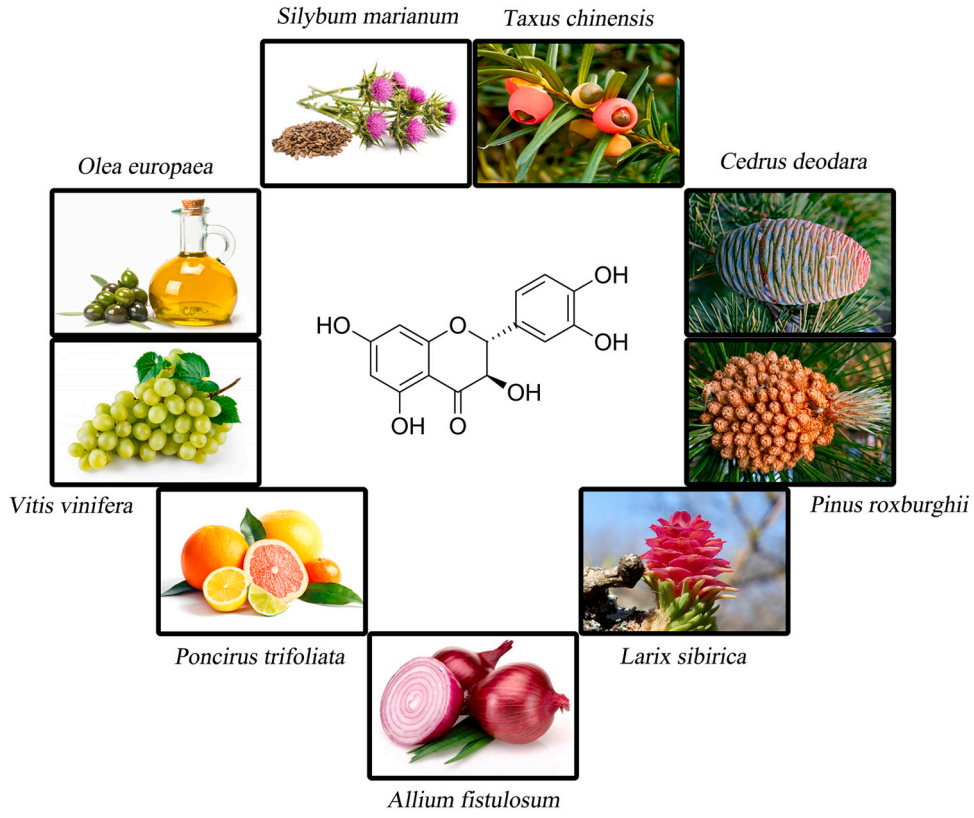

Fig. 1. Natural sources of taxifolin.

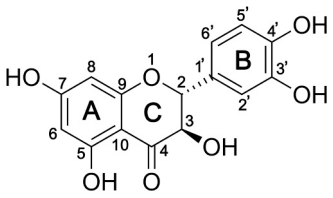

Fig. 2. Structure of taxifolin.

H_2O_2-mediated poly (ADP-ribose) polymerase cleavage through the Nrf2 translocation to the nucleus and the activation of mRNA and protein expression [43]. This showed the protective effect of taxifolin on RPE cells against apoptosis, induced by oxidative stress, through the activation of NRF2 and the phase II antioxidant enzyme system.

3.2. Anti-inflammatory activity

According to the experiment conducted by Wang and his co researchers, taxifolin can regulate the activation of NF-κB in rats diagnosed with cerebral ischemia-reperfusion injury. Furthermore, taxifolin is also associated with the inhibition of leukocyte infiltration and the expression of COX-2 and iNOS in brain [44]. This proves the antioxidant efficacy of taxifolin through the activation of NF-κB pathway. It is also effective against osteoclastogenesis which was examined through both in vivo and in vitro models as well [45]. Recently it has been found that taxifolin causes the inhibition of osteoclastogenesis through RANKL via suppression of the RANKL induced gene expression without significant cytotoxicity that was evaluated via in vitro study [46]. The activation of bone marrow-derived mast cells (BMMCs), rat basophilic leukemia (RBL)-2H3 cells and human mast cell line (HMC-1) by the action of taxifolin was also evaluated in other study. They showed that taxifolin inhibits the degranulation, generation of leukotriene C4 (LTC4), production of interlukin-6 (IL-6), and expression of cyclooxygenase-2 (COX-2) in bone marrow-derived mast cells. Taxifolin also causes the inhibition of RBL-2H3 and HMC-1 cells activation through Akt/IKK/NF-κB and MAPKs/cPLA2 signal pathway [47]. In overall it signifies that taxifolin could become a prospective drug contender for the treatment of allergic and inflammatory diseases. In addition, taxifolin can reduce the inflammation and oxidative stress and triggers autophagy. It is also suggested that taxifolin provides a protective mechanism against the CPF-induced BV2 cell toxicity through the upregulation of pAMPK level along with the activation of Nrf2/HO-1 signaling pathway [48].

3.3. Hepatoprotective activity

Silymarin is a widely used hepatoprotective drug in which taxifolin is found to be an essential component (Legalon®). Several studies have been reported that taxifolin with the doses of 0.25, 0.5 and 1 mg/kg shows significant hepatoprotective activity in rotenone induced hepatotoxic rats. A significant increase in the total protein concentration, bilirubin, activities of alanine aminotransferase (ALT), alkaline phosphate (AKT), gamma glutamyltransferase, and aspartate aminotransferase (AST) has been observed in the taxifolin treated animals [49]. The presence of double bond at C2-C3 position in the C ring of taxifolin is essential for the hepatoprotective activity [50]. Further study showed that taxifolin can prevent the JFH-1 virus-induced oxidative stress on Huh7 human hepatoma cells [51]. Recent research reveals that taxifolin can prevent hepatic injury induced by concanavalin A in mice and also inhibits the TNF-α/ActD induced apoptosis by the regulation of caspase and NF-κB pathways in HepG2 cells [52]. Taxifolin also shows the hepatoprotective activity against acetaminophen induced liver injury in mice through downregulation of TNF-α, IL-6, Bax and increased mRNA expression of Nrf2, SOD2, Bcl-2 and procaspase-3 [53]. Additionally, the hepatoprotective efficacy of taxifolin has also been assessed in mice with carbon tetrachloride induced acute liver injury. Taxifolin decreases the liver lesions, vacuole formation, neutrophil infiltration, necrosis, MDA

levels and increases the activity of antioxidant enzymes [54].

3.4. Anti-Alzheimer activity

Taxifolin is also effective in the treatment of Alzheimer. According to studies, taxifolin, either used alone or in conjunction with cilostazol, significantly reduces elevated αβ and C99 levels in N2a Swe cells. Additionally, it is also associated with the synergistic inhibition of the amyloidogenesis via the downregulation of P-JAK2/P-STAT3-coupled NF-κB linked BACE1 expression through the SIRT1 upregulation [55]. Taxifolin blocks the formation of amyloid-β oligomer, restoring the vascular integrity and memory in cerebral amyloid angiopathy (CAA) [56]. In a recent study by Inoue et al., it is showed that taxifolin increases cerebral blood flow and removes amyloid-β from the brain and inhibits the cognitive dysfunction through the suppression of ApoE–ERK1/2–amyloid-β precursor protein axis [57]. The novel derivatives of taxifolin namely 7-O-cinnamoyltaxifolin and 7-O-feruloyltaxifolin showed significant neuroprotective effects against oxytosis, ferroptosis and ATP depletion in HT22 cell model. The compounds cause the reduction of the LPS-induced neuroinflammation in BV-2 microglia cells. They also showed improved efficacy for short term memory in an AD mouse model, which highlights the neuroprotective activity of taxifolin derivatives [58]. The inhibitory effect of taxifolin on the Amyloid-β-associated neurodegenerative diseases and related disorders has been briefly explained by Tanaka and his fellow researchers [59]. The findings showed the recent advances in taxifolin research based on in vitro*, in vivo* and *in silico* approaches with future research directions for novel therapeutic strategies for CAA, AD, and metabolic diseases with an increased risk for dementia. Furthermore, for the treatment of CAA the implementation of the novel taxifolin has also been well documented by Saito et al. and his co-researchers. In accordance to their study taxifolin facilitated disassembly, prevent oligomer formation and increase clearance of Aβ in a mouse model of CAA with excellent preventive measures for disturbed cerebrovascular reactivity and spatial reference memory impairment in CAA [60].

3.5. Antiangiogenic activity

Taxifolin also showed to have the antiangiogenic activity through the inhibition of the formation of new blood vessels and branches. Taxifolin associated with in vitro antiangiogenic activity by inhibiting the tube formation on Matrigel matrix which was assessed by tube formation assay in human umbilical vein endothelial cells [61].

3.6. Antihyperglycemic activity

The anti-hyperglycemic activity of taxifolin via the modulation of the gastric enzymes and various associated signaling pathways has been established through several studies. In a recent research the ability of taxifolin against postprandial hyperglycemia and α-amylase inhibitory activity was evaluated in alloxan-induced diabetic rat model. The result of the experiment signifies the potent inhibitory activity of taxifolin against α-amylase and the regulation of the postprandial hyperglycemia along with the anti-inflammatory and antioxidant activity during the treatment of DM in rats [62]. Another study evaluated the inhibitory activity of taxifolin against three digestive enzymes both in vitro and in vivo. Taxifolin exerts a potent inhibitory effect against α-glucosidase, α-amylase and pancreatic lipase. Taxifolin acted as the competitive inhibitor of the α-glucosidase and α-amylase, while it was a non-competitive inhibitor of pancreatic lipase. The study reveals that pre-administration of taxifolin noticeably improves the postprandial hyperglycemia and decreases triglyceride absorption by inhibiting pancreatic lipase in rats [63].

3.7. Effect of taxifolin on diabetes related disorders

The function of taxifolin on the metabolism of glucose and water-salt in kidney with metabolic syndrome (MS) rats was evaluated. The results showed that taxifolin significantly opposes the kidney indices and histopathological alterations in MS rats. Along with that taxifolin also increases the protein levels associated with downstream glucose metabolism pathway of PI3K/AKT and maintains the glucose homeostasis with inhibition of RAAS and inflammatory responses [64]. Diabetic retinopathy (DR) is one of the leading causes of blindness. It has been stated that taxifolin provides a protective effect against alloxan-induced DR, in which taxifolin effectively suppressed reactive oxygen species, IL-1b and TNF-a production which demonstrate that taxifolin treatment might be an important choice for the treatment of DR [65]. Taxifolin is also associated with the anti-cataractogenesis activity and could attenuate the diabetic retinopathy in streptozotocin induced diabetic rats. Results from the study suggested that the treatment of the diabetes induced rats with taxifolin showed reduced status of oxidative stress and causes inhibition of p38 MAPK, ERK 1/2 and aldose reductase levels. Treatment with taxifolin also improved the lens opacity in STZ-induced diabetic retinopathy rat models [66].

3.8. Cardiovascular activity

Hyperlipidemia is the most crucial factor for the development of atherosclerosis and coronary heart disease due to increase in the cholesterol or LDL cholesterol level. Several studies have showed that taxifolin possesses anti-hyperlipidemic activity which has been evaluated by the assessment of the hyperlipidemic rats treated with taxifolin. Results showed that taxifolin maintains the normal lipid profile in the serum and liver, and lipid excretion in fecal of rats, which has been supplemented with cholesterol rich diet [67]. The result from the in vivo study also reveals that taxifolin treated animals showed lower levels of total liver cholesterol along with the reduction in thiobarbituric acid reactive substance levels in both serum and liver [68]. In a study it has been shown that the pretreatment of HepG2 cells with taxifolin causes the inhibition of the cholesterol synthesis along with the reduction of the HMG-CoA reductase activity. Taxifolin also causes the suppression of esterification of cellular cholesterol, triacylglycerol and phospholipid syntheses. In addition, taxifolin reduced the hepatic lipid synthesis via altering the secretion of apoB and apoA-I [69]. Currently taxifolin has been reported to inhibit the stress induced apoptosis, mainly oxidative stress and endoplasmic reticulum stress, via the PI3K/Akt pathway, which provides the cardioprotective activity against ischemia-reperfusion injury. Furthermore, taxifolin also delays the onset of endoplasmic reticulum stress by regulating certain protein expression [70]. In another study, taxifolin has been evaluated to identify the effect and mechanism on myocardial ischemia/reperfusion (I/R) injury. Taxifolin improved the ventricular functional recovery and the levels of SOD, GSH-PX. The upregulation of antiapoptotic proteins such as Bcl2 and downregulation of proapoptoic proteins (Bax, Cyt-c, caspase 3 and 9) was shown, that leads to the inhibition of the myocardial apoptosis by the action of taxifolin. As a result it was proved that taxifolin significantly improved the cardiac function and regulated oxidative stress and attenuated apoptosis [71]. Besides the regulation of lipid profile taxifolin has also been found to act on the several pathways to regulate the blood pressure and showed antihypertensive activity. Taxifolin has been found to have the capacity to lower blood pressure and to improve endothelial function. Bernatova and Liskova documented all the possible mechanisms from preclinical studies through which taxifolin showed its antihypertensive activity in the cardiovascular system mainly via endothelial NO production, and the reduction of ACE activity and iNOS expression. Additionally, it also protects the endothelial function and thus participated in the blood pressure regulating mechanisms in various experimental hypertension models [72].

3.9. Antimicrobial activity

The antimicrobial activity of taxifolin has been evaluated in several studies. The sensitivity of *Escherichia coli* VL-613, *Staphylococcus epidermidis* ATCC 14990, *Pseudomonas aeruginosa* 98, *M. luteus* ATCC 10240, *Micrococcus luteus(lysodeicticus)* ATCC 4698 towards taxifolin was evaluated using gel dilution test and it was showed that *S. epidermidis* was highly sensitive against 5.0% of taxifolin with zone of inhibition 21.33 ± 0.82 mm [73]. Taxifolin also have antimicrobial effect against dental pathogens such as *S. sobrinus*. It also inhibits the growth of *S. sobrinus* and glucosyltransferase [74]. Additionally, taxifolin is also effective against *M. tuberculosis* H37Rv, which was assessed via in silico molecular docking and dynamics stimulation showing a significant interaction with active amino acids of Mtb DNA gyrase and isoleucyl-tRNA synthetase [75]. Metsämuuronen and Sirén have documented the antibacterial activity of bioactive phenolics compound including taxifolin along with the biosynthetic pathway of each active component and also compared to establish the most effective secondary metabolites [76].

3.10. Anti-psoriatic activity

Psoriasis is a T cells mediated chronic skin inflammation, which plays a vital role in the pathogenesis of the disease. Taxifolin has potential activity against psoriasis and it effectively inhibits the LPS-induced abnormal proliferation in Hacat cell line and attenuates significantly the IMQ-induced psoriasis in BALB/c mice. Taxifolin also regulates the T_h cells differentiation through the inhibition of several transcription factors such as T-bet, GATA-3 and RORγt. Along with that it also caused the inhibition of Notch1 and Jak2/Stat3 signal pathways which in turn alleviates psoriasis condition [77].

3.11. Anti-hyperuricemic activity

Hyperuricemia is considered as the pivotal risk factor for gout. Generally high intake of the purine containing foods such as meats and sea foods causes high levels of uric acid in blood. In a study the anti-hyperuricemic activity of taxifolin was evaluated in both cultured AML12 hepatocytes and hyperuricemic model mice. According to this study taxifolin causes a significant suppression of uric acid production in a dose and time-dependent manner in the cultured hepatocytes. Taxifolin suppresses the uric acid level in serum and liver in guanosine-5'–monophosphate and inosine-5'–monophosphate induced hyperuricemic mice model. Taxifolin also suppressed the hepatic xanthine oxidase activity [78]. These findings indicate that taxifolin has a potent hypouricemic function and may be a promising anti-hyperuricemic phytochemical agent.

3.12. Pulmonary activity

Taxifolin also possesses the activity against the pulmonary damage. The effect of taxifolin was investigated in cisplatin-induced pulmonary damage by biochemical and histopathological assessment in male albino Wistar rats. The results from the biochemical and histopathological analysis showed that the taxifolin treated animals were healthy and there was no sign of oxidative pulmonary damage as compared to the cisplatin treated group. These findings suggested that taxifolin might be effective in the treatment of cisplatin induced pulmonary toxicity [79].

3.13. Genotoxic activity

The genotoxic activity of taxifolin has been evaluated by Zhanataev and associates through DNA-comet assay and chromosome aberrations counting. This suggested that taxifolin treated animals were not associated with any sort of DNA damage in mouse bone marrow, blood, liver, and rectal cells. Taxifolin treated mouse bone marrow cells didn't show any sign of chromosome aberrations. Taxifolin also have antifibrotic effect, evaluated on prostatic gland in rats, which suffers from chronic nonbacterial inflammation [80].

3.14. Antiviral activity

The antiviral activity of taxifolin has been also explored recently against severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) causing COVID-19. After vigorous *in silico* study the researchers found that taxifolin could be a potential inhibitor against SARS-CoV-2 main protease with lowest predicted IC50 value among a number of flavonoids [81]. Another group of researchers also performed extensive computational screening for the discovery of SARSCoV-2 main protease inhibitors and they found 11 potential binders among which taxifolin is one of them. They also estimated low to moderate toxicity caused by off-target binding, improved drug-likeness, as well as enhanced binding to the therapeutic target compared to the cocrystallized ligand [82]. These data show that taxifolin is a possible anti-SARS-CoV-2 medication that will require preclinical testing before being approved as an anti-covid-19 medicinal molecule.

3.15. Antifungal activity

The antifungal activity of taxifolin has also been evaluated through various studies. According to the previous research the antifungal activity of taxifolin was being assessed in five different fungal species such as *Alternaria alternata (Fr.) Keissler, Aspergillus fumigatus Fresenius, Aspergillus niger van Tieghem, Macrophomina phaseolina (Tassi) Goid., and Penicillium citrii.* They were treated by different concentrations (100, 300, 500, 700, 900, and 1000 ppm) of taxifolin which showing as excellent antifungal activity through the significant inhibition of fungal growth in a dose dependent manner [83].

3.16. Chemotherapeutic activity

3.16.1. Breast cancer

Breast cancer is the most common form of cancer in women and the leading cause of cancer related death. In 2018, there were 2,088,849 new cases of breast cancer that have been identified globally, which results in 626,679 deaths [84]. Breast cancer is expected to become more prevalent in India, rising from 203.5 per 100,000 females in 2011 to 233 per 1000 females in 2026 [85]. As a result, it is clear that novel therapeutic initiatives for breast cancer control in the country are urgently needed.

Breast cancer is caused by uncontrolled growth of breast cells, most commonly originate from the inner lining of the milk ducts or the lobules, due to mutations in the genes that regulate breast cell proliferation [86]. In a cancer microenvironment, for the rapid proliferation of the cancer cells required high lipogenesis and glucose consumption rate. There are several oncoproteins and a number of oncological signaling pathways which can modulate the expression of different lipogenic and glycolytic enzymes and eventually increases the glucose consumption and fatty acid synthesis at the primary stage of cancer development [87].

The de novo fatty acid that synthesized is required for the formation of the membrane building blocks, signaling mediators, protein modifying lipids which are essential for the structural modifications, resistance, signal transduction, intracellular trafficking and cell migration for cancer cell survival and progression [88]. It was showed that the expression of the 3-hydroxy-3-methylglutaryl-coenzyme A reductase (HMG-CoAR) significantly increased in the in neoplastic cells which aids the cholesterol uptake and synthesis [89]. Liver X receptors (LXR α & β), an important target for cancer chemotherapy, associated with the maintenance of the intracellular cholesterol homeostasis and its efflux [90]. The functionality of this nuclear receptor is regulated by oxysterol ligands which are synthesized from cholesterol [91].

In a study, the effect of taxifolin has been evaluated against the mammary cancer through interrupting the carcinogen induced lipid and carbohydrate metabolism (LXR agonist and HMG-CoAR antagonist activity). Study revealed that taxifolin restored the altered metabolism through interacting with the LXRs, HMG-CoAR and inhibits the uncontrolled cell proliferation [92].

Epithelial-to-mesenchymal transition (EMT) and its reversed process, mesenchymal-to-epithelial transition (MET), are elementary processes associated with normal biological development and disease progression [93]. During the EMT process the epithelial cancer cells loses their apical-basal polarity, cell-cell adhesion and basement-membrane and change to mesenchymal like cells, acquiring increased cell polarity and motility potential [94]. This process is associated with the decreased expression of E-cadherin and Claudin (epithelial markers) and increased expression of the N-cadherin and Vimentin (mesenchymal markers) [95]. Activation of EMT is mainly regulated by various EMT-activating transcription factors (EMT-TFs) such as Snail, Twist and ZEB families and various signaling pathways including Hedgehog (Hh), Wnt/β-catenin, Notch and transforming growth factor-β (TGF-β), which ultimately possesses the pivotal role from cancer initiation to metastasis [96,97].

Taxifolin plays a vital role in mitigating the cancer cell proliferation, migration and invasion in aggressive breast carcinoma which has been evaluated through in vivo and in vitro assessment. According to the results from the studies taxifolin strongly inhibits the cancer cell proliferation, migration in a dose dependent manner. Additionally, it prevents the EMT process, decreases the expression of mesenchymal markers and promoted MET (Mesenchymal to epithelial transition). It also decreases the protein and mRNA expressions of β-catenin. In addition it inhibits the growth of primary tumors and prevents the lung metastasis of breast cancer as evaluated in 4T1 xenograft mouse model [98].

The activation, metabolism and detoxification of xenobiotics is mainly regulated by cytochrome P450s (CYPs), a class of hemeproteins containing enzymes [99]. CYP1A1, CYP1B1, and CYP1A2 are the subfamily of human CYP1, among which only CYP1A1 participates in the metabolism of procarcinogens like polycyclic aromatic hydrocarbons (PAH). On the other hand, CYP1A1 and CYP1B1 are the extrahepatic enzymes, involving in the cancer initiation and progression while CYP1A2 only expressed in liver [100–102].

The expression of CYP1A1 and CYP1B1 is regulated through AhR, a member of basic Helix–Loop–Helix (bHLH)/Per–Arnt–Sim (bHLH/PAS) of a protein family [103]. It is a ligand-dependent transcription factor, which binds with the xenobiotic responsive elements to the DNA and inhibits the AhR transcription.

Several studies have been reported that AhR, CYP1A1, and CYP1B1 are well marked promoters of breast cancer as well as lung cancer [104–106]. Furthermore, it was showed that the expression of CYP1A1 and CYP1B1 upregulated in several breast cancers [107] and CYP1A1 expression mainly regulates the proliferation and survival of breast cancer cells [104]. Previous study reveals that the expression of AhR was also upregulated in breast cancer [108].

The potential chemotherapeutic activity of taxifolin against DMBA induced breast cancer has also been evaluated in Sprague–Dawley rats. In this research they have showed the alteration of energy regulation by taxifolin on the carcinogen treated rats through significant restoration of the cancer induced modification which facilitates tumor growth. Taxifolin also causes the downregulation of the expression of CYP1A1 and CYP1B1 via inhibiting AhR signaling pathway [109]. This suggested that TAX could be used as a chemotherapeutic agent against CYP1A1 and CYP1B1-mediated cancers, as well as inhibiting DMBA-induced mammary carcinogenesis in a rat model.

3.16.2. Lung cancer

Lung cancers, more specifically non-small cell lung cancer (NSCLC) is responsible for the large majority (85%) of lung cancer related death worldwide, in both men and women [110]. A large number of patients are already diagnosed with cancer metastasis and as a consequence the five-year survival rate of the patients is less than 20% [111,112]. This situation suggested that administration with proper classification and early diagnosis is needed desperately which enables the development of more targeted chemotherapies for the NSCLCs [113].

Cancer stem cells (CSCs) are the special type of cells that contains the stem like properties. These stem cells are mainly responsible for tumor growth, cancer recurrence, drug resistance and cancer metastasis through epithelial-to-mesenchymal transition (EMT) [114]. There are some signal transduction pathways which could be potential targets for the therapy of NSCLCs, which include VEGF, p38 MAPK, Wnt, NF-κB, and PI3K signaling pathways and current immune checkpoints [115,116].

Taxifolin has been reported to inhibit stemness and EMT directly and indirectly in several tumor related studies. Taxifolin causes the modification of various bioactive materials and promotes the differentiation of mesenchymal stem cells, which are derived from human umbilical cord into osteoblasts [117]. It has also been documented that taxifolin enhances the inhibition of the NF-κB signaling pathway associated with the osteogenic differentiation. There are various signaling pathways which involved in the regulation of stemness such as Janus family tyrosine kinase (JAK)/signal transducer and activator of transcription (STAT), Notch, PI3K/AKT serine/threonine kinase, SHH, and Wnt/β-catenin pathways [114].

Several researches showed that taxifolin involves in most of the signaling pathways associated with stemness regulation [118–120]. Furthermore, taxifolin significantly reverse the process of EMT and promoted MET in breast cancer through the inhibition of β-catenin signaling pathway [98]. In a research, the effect of taxifolin has also been evaluated in relation to its stemness inhibitory activity in two lung cancer cell lines, A549 and H1975, and in A549 xenografts. This suggested that taxifolin causes the inhibition of stemness by downregulating the protein expression of SOX2 and OCT4, and reduced CD133-positive cells. Taxifolin also inhibited the invasiveness of the cancer stem cells and the expression of N-cadherin and vimentin with upregulating the expression of E-cadherin. This indicates the inhibition of EMT by the action of taxifolin. In A549 xenograft BALB/c mice, it suppressed the tumor growth with decreased expression of SOX2 and OCT4 and inhibited PI3K, TCF4 protein phosphorylation [121].

3.16.3. Colorectal cancer

Colorectal cancer (CRC) is the most diagnosed cancer in men than in women worldwide. It is estimated that about 1,096,000 new incidents of colon cancer to be diagnosed in 2018 and about 704,000 new cases of rectal cancer are expected. All together these comprise 1.8 million new cases of CRC [122].

Recent study investigated the inhibitory effect of taxifolin in colon cancer cell lines and in HCT116 xenograft model. It was revealed that taxifolin possesses cytotoxicity in colorectal cancer cell lines (HCT-116 and HT-29) in a dose and time dependent manner. Administration of taxifolin in colorectal cancer cell lines causes the arrest in cellular growth, alteration of the molecules which regulates the G2 phase, and induced apoptosis in a dose dependent manner. Taxifolin also decreased the expression of β-catenin, AKT and survivin genes and protein expression in both in vitro and in vivo [120]. These findings suggested that targeting the β-catenin gene could promote cell cycle and cell cycle regulator changes as a result of taxifolin treatment, thus lowering the risk of colorectal cancer.

3.16.4. Liver cancer

Liver cancer or hepatocarcinoma is one of the most frequently occurring cancer and leading cause of cancer related death in men. In 2020, the number of new cases was found to be 905,677 and the number of new deaths 830,180 [123].

In several past studies it was reported that the polyphenols and other

natural compounds have the potential to regulate the microRNA (miRNA) expression [124–126]. Lee et al. first described the miRNA [127]. An interesting fact about miRNA is, it is capable of regulating a number of target proteins as well as several miRNA molecules can target the same protein and can modulate [128,129]. Various researches have demonstrated the miRNA as tumor compressor or oncogene through the assessment of their rate of expression and activity on various protein targets [130]. A transcription factor, ZEB2 protein or Zinc finger E-box-binding homeobox 2 or SIP1 [131,132], plays an important role in EMT which is regulated by several transcription factors including ZEB, Snail or Twist, and epigenetics [133]. There are several miRNAs which can directly regulate the expression of ZEB2 protein such as miR-30a, miR-141, and miR-335 [134–136].

In a recent study the effect of taxifolin on the expression of majority human miRNAs was evaluated through Affymetrix GeneChip™ miRNA 3.0 Array on two cell lines, Hep G2 and primary human hepatocytes. According to this study the expression of four miRNAs, miR-153, miR-204, miR-211, and miR-377-3p, was downregulated due to the treatment with taxifolin. Interestingly all of these miRNAs were directly linked with the expression of ZEB2 protein in different cancer model systems. Additionally, the treatment with taxifolin causes dose dependent upregulation of the ZEB2 protein expression. Taxifolin also inhibits the Akt phosphorylation and thus diminishing ZEB2 signaling which in turn triggers the carcinogenesis. This result suggested that taxifolin has confusing or even conflicting outcomes due to non-specific effects on the cell [137].

3.16.5. Prostate cancer

Prostate cancer is the second most common form of cancer occurring in men and fifth leading cause of cancer related death worldwide. Prostate cancer is frequently asymptomatic at early stage and has an indifferent prognosis, requiring just active observation. The most common complications associated with the prostate cancer include difficulty with urination, increased frequency, and nocturia which basically originates from prostatic hypertrophy. In more advance stages it may be associated with urinary retention and back pain, because the axis skeleton is most relevant site for bony metastatic disease. According to the estimation from GLOBOCAN 2018, the number of new cases of prostate cancer was reported to be 1,276,106 worldwide in 2018, with maximum incidence in the developed countries [138].

Several studies have demonstrated the full spectrum of taxifolin's anticancer efficacy in various cancer model systems [120,121,137] but the combination of taxifolin with other flavonoids has not been reported often. In a recent study the effect of taxifolin in conjunction with andrographolide (Andro), a diterpenoid lactone isolated from the functional herb *Andrographis paniculata*, on the prostate cancer was evaluated in prostate cancer DU145 cells. The study showed the effect of Andro in the inhibition of the prostate cancer cell proliferation via arrest of the mitotic phase and triggering of the intrinsic apoptotic pathway. The use of the taxifolin and Andro in combination significantly potentiates the antiproliferative effect by enhanced mitotic arrest and apoptosis through the cleavage of poly (ADP-ribose) polymerase, and caspases-7 and -9. Taxifolin in association with Andro also increased the in vitro microtubule polymerization, along with the formation of twisted and elongated spindles in the cancer cells, ultimately causing mitotic arrest. The diminution of MAD2, a component in the spindle assembly checkpoint (SAC), improved the mitotic block, causing the activation of SAC which leads to the mitotic arrest. In overall it was suggested that the taxifolin and andrographolide combination treatment could activate the SAC and thus disrupts the microtubule dynamics [139].

The lowering of the circulating testosterone level by chemical induced castration is an essential approach for the treatment of prostate cancer. Testicular Leydig cells are mainly responsible for the biosynthesis of androgen from cholesterol [140].

Several flavonoids have been reported which blocks the biosynthesis of androgen [141,142]. It was found that taxifolin is a potential agent which blocks the biosynthesis of androgen. Taxifolin decreased basal, LH-stimulated, 8BR-stimulated, pregnenolone-mediated, and progesterone-mediated androgen production by Leydig cells significantly. Taxifolin also inhibited 3β-hydroxysteroid dehydrogenase and 17α-hydroxylase/17, 20-lyase enzyme activities in rat as well as in human testis. These findings established taxifolin as a potential competitive inhibitor of these two enzymes which could play a significant role in the treatment of prostate cancer [143].

3.16.6. Bone cancer

The initiation of bone cancer or osteosarcoma occurs predominantly in the metaphysis of the long bones generally in children and young adults. It starts as a monoclonal disease and develops as a polyclonal disease so fast. A large heterogeneity found in osteosarcoma which was showed in a exome sequencing study involving multiple pathways [144]. Osteosarcoma is basically a vascularized tumor which is characterized by typical osteoid matrix formed by cancer cells [145]. Primary bone cancers include osteosarcoma, Ewing sarcoma, and chondrosarcoma. They account for less than 1% of diagnosed cancers each year and are associated with significant morbidity and mortality [146]. It is the most common form of cancer, responsible for nearly two-thirds of all cases [147].

In a study the anticancer effect of taxifolin against osteosarcoma has been evaluated on U2OS and Saos-2, human osteosarcoma cancer cell lines. The taxifolin treatment caused a dose dependent antiproliferative effect with reduced colony formation efficiency. The tumor growth was significantly inhibited due to introduction of taxifolin in U2OS xenograft nude mice. Taxifolin also endorsed the G1 cell cycle arrest and induction of apoptosis in U2OS and Saos-2 cell lines. Treatment with taxifolin also caused a significant downregulation of the expression of AKT serine/threonine kinase 1 (AKT), phosphorylated (p-Ser473) AKT, v-myc avian myelocytomatosis viral oncogene homolog (c-myc) and S-phase kinase associated protein 2 (SKP-2) levels in both the cell lines. These outcomes suggested that taxifolin disrupts the cellular migration and invasion which markedly associated with the decrease in SKP-2 overexpression and presented itself as a potential contender in the treatment of osteosarcoma [148].

3.16.7. Skin cancer

Skin cancer is the one of the most common form of cancer incidence worldwide. Skin cancer is generally caused most frequently due to the continuous exposure to the sunlight, also due to the climate change and even due to the change in the thickness of protective ozone layer [149]. Skin cancer can be classified into two subtypes: Melanoma Skin Cancer (MSC) and Non-Melanoma Skin Cancer (NMSC) [150]. Non-melanoma cancer can be divided into two types: basal cell carcinoma (BCC) and squamous cell carcinoma (SCC) [151]. Basal cell carcinoma responsible for 80% of non-melanoma skin cancers and malignant melanoma responsible for 1% of skin cancer which causes of 60% of mortality [149].

UV radiation triggers epidermal growth factor receptor (EGFR), a member of receptor tyrosine kinase, which is activated and/or over expressed in various human cancers including UV-induced skin cancer [152,153]. Activation of EGFR is associated with the further downstream activation of several signaling cascade including extracellular regulated kinases (ERKs), p38 kinase and c-Jun NH2-terminal kinases (JNKs), cell division regulators [154–156]. It also caused the activation of phosphatidyl inositol-3-kinase (PI3-K), which leads to activation of Akt and inhibition of apoptosis [157]. Thus, the EGFR and PI3-K/Akt signaling pathways are the most effective molecular targets for the prevention of UV-induced skin cancer.

Prevention of skin cancer has also been reported as one of anticancer activities of taxifolin. From the *in silico* study, it has been reported that EGFR, phosphatidyl inositol 3-kinase (PI3-K) and Src are very potential targets for the taxifolin. In the research it was showed that taxifolin bound to EGFR and PI3-K at the ATP binding pocket and inhibited their

kinase activities. Taxifolin also associated with the suppression of the UVB-induced activation of EGFR and Akt and prevented downstream signaling cascade in JB6 P+ mouse skin epidermal cells. Taxifolin also attenuated the expression of COX-2 and prostaglandin E2 (PGE2) induced by UVB and also inhibited the cellular transformation induced by EGFR. Topical application of taxifolin suppressed tumor incidence, volume and multiplicity in mouse model which suggested the chemopreventive activity of taxifolin against the UV-induced skin cancer by EGFR and PI3K targeting [158].

There are various factors which are responsible for the cancer development and scar, caused by vaccines, burns, and other injuries, that could also lead to cancer development. Those cancers are known as scar carcinoma and generally occur on skin tissue [159]. The anticancer activity of taxifolin against skin scar cell carcinoma (SSCC) has been evaluated which demonstrated that taxifolin effectively inhibit the development of SSCC through apoptosis and cell cycle arrest. Taxifolin also suppressed the invasion of SSCC through the downregulation of matrix metalloproteinases (MMP) MMP-2 and MMP-9 expression [160]. Taxifolin was discovered to inhibit the growth of SSCC by inducing apoptosis and cell cycle arrest, along with suppressing cell invasion.

3.16.8. *Taxifolin and drug resistance*

The multi drug resistance (MDR) has been found to be one of the major causes of chemotherapy failure. The increased efflux through ATP-binding cassette (ABC) efflux transporters has been reported to be the primary mechanism which enables the drug resistance by decreased cellular accumulation of the drug [161]. P-glycoprotein (P-gp), encoded by ABCB1 gene, is the vital efflux transporter, among the ABC transporters for a number of chemotherapeutic agents. P-glycoprotein (P-gp), a 170 kDa efflux membrane transporter, abundantly present throughout the human body (intestines, placenta, kidney, liver and blood–brain barrier). In a healthy cell, P-gp inhibited the entry of carcinogens, toxins, and other xenobiotics [162]. Despite all of the benefits of P-gp, the overexpression often leads to the MDR phenomena [163]. Recently nuclear factor erythroid 2-related factor 2 (Nrf2) has been reported to be responsible for the development of chemoresistance [164]. Nrf2 is mainly associated with the management of antioxidant activity through the regulation of oxidative stress and other kind of stresses [165–167]. Nef2 exerted the chemoresistance through upregulating the expression of CD99 [168], inhibition of DNA damage [169], and the reduction of the oxidative stress mediated damage [170].

The effect of taxifolin on the human P-gp activity has been assessed in a previous study. The transporter inhibition activity was evaluated on the human P-gp stable expression cells (ABCB1/Flp-InTM-293) along with the MDR reversal activity of taxifolin on the human cervical carcinoma cell line HeLaS3. The outcome of the study illustrated the dose dependent decrease of ABCB1 expression due to taxifolin treatment. Taxifolin also inhibited the activity of P-gp via uncompetitive inhibition of rhodamine 123 and doxorubicin efflux which suggested significant resensitization of MDR cells to the chemotherapeutic agents [171]. These findings indicated that taxifolin could be used as a synergistic treatment for MDR cancers as a P-gp modulator.

The primary anticancer activity of taxifolin (Fig. 3) is associated with the regulation of β-catenin and PI3K pathway which modulates a number of cancerous conditions.

It has been found that taxifolin mainly binds with two specific molecular targets in a cancer microenvironment, PI3K and EGFR [158], and regulates a number of signaling pathways and the expression of different

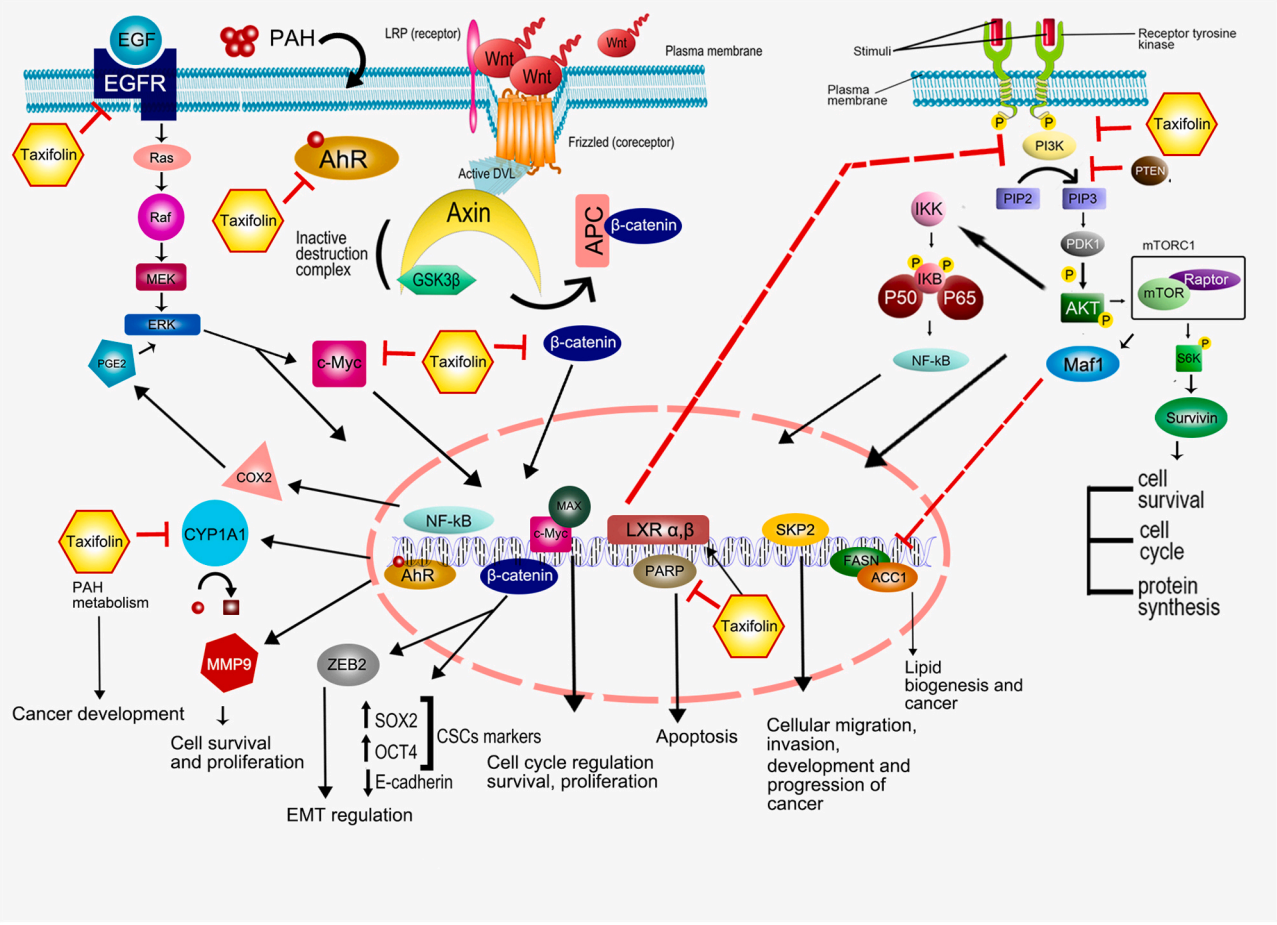

Fig. 3. Graphical summary of anticancer mechanism of taxifolin.

proteins. After analyzing all the data mentioned above the regulation of EMT and stemness has been found to be most prominent role of taxifolin in various cancer models. The stemness and EMT is mainly regulated by the β-catenin and PI3K pathway which causes the overexpression of stem cell markers such as SOX2 and OCT4 and mesenchymal cell markers (N-cadherin and vimentin) [114,172]. It has been observed that the activation of PI3K/AKT pathway and β-catenin accumulation in tumors is often associated with mutational inactivation of the p53 tumor suppressor [173,174] which disrupts the apoptosis of cancer cells. In addition, there is a relation between Wnt and EGFR signaling in cancers suggesting that Wnt ligands can activate EGFR signaling while EGFR can activate β-catenin via receptor tyrosine kinase-PI3K/Akt pathway; EGFR has been shown to form a complex with β-catenin and increase the invasion and metastasis of cancer cells [175]. Taxifolin treatment leads to the inhibition of the expression of these proteins and prevents the cancer progression, metastasis, cancer relapse and promotes apoptosis. Besides that, regulation of these signaling pathways leads to the alteration of various other protein molecules such as SKP2, LXR, survivin, ZEB2, c-Myc and others which are related to cancer development and progression in different tissues. Additionally, chemotherapeutic activity of taxifolin is also associated with the re-sensitization of resistant cancer cells through the inactivation of P-gp and preventing the drug efflux from the cancer cells.

4. Clinical study

A number of human studies have been performed for taxifolin on the human subjects with different physiological conditions [37]. Most of these studies were carried out in Russian Federation. The taxifolin utilized in these researches was made using the same or very identical methods as the intended product. As a result, it's safe to believe that taxifolin's purity was high, with just low quantities of contaminating compounds, identical to the intended product. Altogether, 507 patients were treated with taxifolin from larch wood (40–120 mg/day) for 2 weeks – 3 months. At the end of the human study no side effects were found in the taxifolin group [176,177]. From the human and animal studies it was evaluated that taxifolin can be added in the pre-packed foods to cause a health benefit as antioxidant and anti-inflammatory agent which is supported by the various in vivo and in vitro studies. Additionally, the safety of taxifolin has been demonstrated in several animal and human studies, and it is also reinforced by the widespread usage of taxifolin in human food in countries outside of the EU, such as Russia and the United States. These evidences provided strongly suggests that taxifolin could be used as a novel dietary additive. Another clinical has been recently in process regarding the effect of the dietary supplement taxifolin aqua on the recovery period after COVID-19 pneumonia. The primary objective of this trial is to monitor the effect of taxifolin aqua therapy on the indicators of respiratory function, the state of the arterial wall, the contractile function of the myocardium, as well as to assess the effect of Taxifolin Aqua therapy on markers of biological age, quality of patient's life. This study will be performed by using 100 patients (30 mg per day with standard therapy) who had covid pneumonia 3 months ago. Patient monitoring will be carried out within 2 months from the date of inclusion. A follow-up visit is scheduled in 2 months. During the study, the patient will be regularly monitored for tolerance and safety of therapy with Taxifolin Aqua [178].

5. Market place, clinical medicine and possible drug targets

Taxifolin is used as food ingredient in various markets of E.U. They are generally intended as food supplements or in PARNUTs. Taxifolin is intended for use as a food for particular nutritional uses (PARNUTS) (Council Directive 89/398/EEC) (Council of the European Communities, 1989), such as, a food for special medical purposes (Commission Directive 1999/21/EC) (Commission of the European Communities, 1999) and a food intended to meet the expenditure of intense muscular effort, especially for sportsmen. Taxifolin can also be used along with vitamins such as Vitamin C to enhance its efficacy. Vitamin C tablets with enhanced dihydroquercetin are already being sold in the market [179]. Taxifolin also shows its activity immuno booster. The immunity is significantly enhanced due to taxifolin intake as a food supplement [180]. The proposed daily intake is 100 mg taxifolin/day. Taxifolin is a powerful flavonoid with therapeutic potential in the treatment of illnesses, particularly cancer-related inflammation. Over the last half-decade, taxifolin has become more widely used in pharmaceuticals and healthcare. Aside from its health benefits, taxifolin progressively penetrated in the cosmetics market for its delayed skin ageing property.

Furthermore, the clinical medications can be developed from the drug targets for taxifolin. Taxifolin acts on the EGFR and PI3K receptor as an antagonist shows a number of chemotherapeutic activities including antiproliferative, antiangiogenic, stemness and EMT regulation on various cancer model systems. Taxifolin also acts on through ARE-set up process to regulate gene expression and shows excellent chemopreventive activity [181]. The anti-inflammatory, antioxidant, and vascular-defensive properties of this compound are its great attributes. It inhibits the activity of COX-2 and shows its anti-inflammatory activity in animals and human [182]. Taxifolin is said to improve the efficacy of standard antibiotics like ceftazidime and levofloxacin in vitro, allowing for the provision of combinatorial therapy to patients with methicillin-resistant Staphylococcus aureus (MRSA) infections [183]. Recently, molecular docking study confirmed that taxifolin has been shown to interact with SARS-CoV-2 main protease (M^{pro}) which supports its antiviral activity against severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) causing COVID-19 [81].

6. Limitations and overcome

Taxifolin is a flavanonol with a unique structure that makes it exceptional to other flavonoids in terms of antioxidant activity but its limited bioavailability is a key barrier for biological applications. Due to slight solubility of taxifolin (0.1% at room temperature) [184,185] it is very difficult for taxifolin to be absorbed and metabolized by the body which significantly limits its bioavailability and efficacy [186,187]. It has also been showed that taxifolin has limited efficacy to cross the blood brain barrier (BBB) which limits its activity against the intracerebral amyloid-β aggregation [56]. In order to increase the bioavailability, solubility and permeability of taxifolin micronization technology should be used to generate microscopic and uniform amorphous taxifolin nanoparticles [188].

7. Conclusion

Researchers are increasingly showing interest in chemical compounds produced from natural sources, particularly plant-derived compounds, because of their multiple chemotherapeutic and pharmacological properties that improve human health. Flavonoids, a plant-derived substance, were found to be extremely effective for the treatment of a variety of ailments, including cardiovascular disease, pulmonary disease, hepatic abnormalities, diabetes, and others with fewer side effects than synthetic molecules, which increased the popularity of these chemicals among medicinal chemists, pharmacologists, and dieticians. In addition, because of their abundance, acceptance, affordability, and safety for frequent use, these phytochemicals can be employed as a supplemental therapy to protect and decrease the progression of human cancer.

Several studies have been performed on the taxifolin and numerous pharmacological properties (Fig. 4) have been observed including antioxidant, anti-inflammatory, hepatoprotective, anti-Alzheimer's, antiangiogenic, antihyperglycemic, cardiovascular disorder, antimicrobial, antipsoriatic, antihyperuricemic, pulmonary, genotoxic activity and anticancer activity.

The primary action of taxifolin is associated with the inflammatory

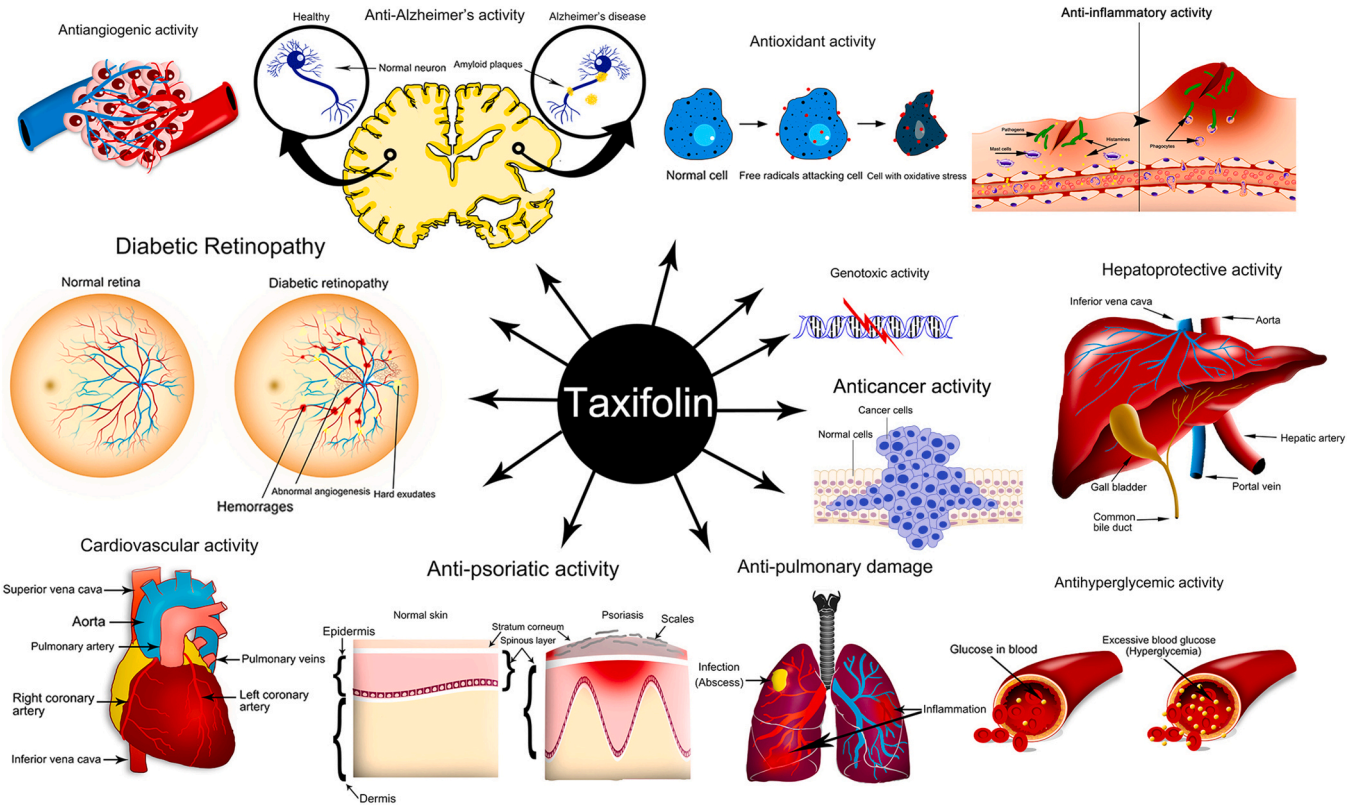

Fig. 4. Schematic representation of pharmacological activities of taxifolin.

responses, oxidative stress and the protection of the vascular wall. From the SAR of taxifolin it has been well defined that the structural orientation of taxifolin makes it capable of scavenging the free radical which corresponds to its antioxidant efficacy. Taxifolin causes the inhibition of the lipid peroxidation, H_2O_2-induced poly (ADP-ribose) polymerase cleavage and results in excellent antioxidant activity. Besides, taxifolin also bind with several molecular targets that are responsible for inflammatory response such as COX-2, interlukin-6 (IL-6), iNOS, RANKL through Akt/IKK/NF-κB, MAPKs/cPLA2, Nrf2/HO-1 pathways and provide benefits for cardiovascular health, the pores and skin, cognitive feature, contamination, allergic reactions and immunodeficiency. Additionally, these activities are also responsible for lowering blood viscosity, improvement of capillary microcirculation, protection of vascular complication, prevention of macular degeneration through the inhibition of pro-inflammatory cytokines. Taxifolin also has the neuroprotective role through the inhibition of the enzymes responsible for the infection and inflammatory response to the brain stem which justifies the anti-Alzheimer's activity as well. In-depth research into taxifolin's biochemistry and mechanism of action on oxidative stress and inflammation-related components could be crucial in improving its bioaccessibility and bioavailability as a medication.

Due to this widespread bioactivity of taxifolin it has an interesting market place from food supplements to chemotherapeutic medication. A number of human studies of taxifolin activity at different physiological condition confirm its non-toxic characteristic with excellent bioactivity. These bioactivities enable the use of taxifolin as a potential food supplement as an antioxidant, immuno booster, cardioprotection for sportsman. Recently, the protective role of taxifolin as dietary supplement on recovery period after COVID-19 Pneumonia is being assessed through clinical trial. Additionally, the inhibitory activity of taxifolin against COVID-19 by acting on the SARS-Cov2 Main protease (M^{pro}) has been identified through virtual screening.

Overall, the present study provides comprehensive update on therapeutic potential of taxifolin which may foster the discovery and development of an outstanding novel therapeutic entity which will surely accelerate the transformation of the molecule from dietary food to a multifunctional drug molecule in the near future.

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Abhijit Das: Article writing, Processing of illustration. **Ratna Baidya:** Data collection. **Tania Chakraborty:** Research design, Conceptualization. **Akash Kumar Samanta:** Organization, Data collection. **Souvik Roy:** Revision of article, Final approval.

Conflict of interest statement

The authors declare that they have no conflict of interest.

Data availability

Data sharing is not applicable to this article as no datasets were generated or analyzed during the current study.

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