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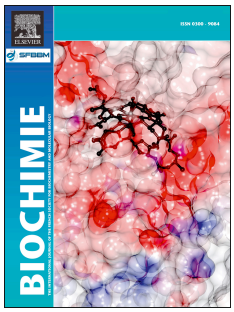

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Targeting signal transducers and activators of transcription (STAT) in human cancer by dietary polyphenolic antioxidants

Hamed Amani [1#], Marjan Ajami [2#], Solmaz Nasseri Maleki [3], Hamidreza Pazoki-Toroudi [3], Maria Daglia [4]*, Arold Jorel Tsetegho Sokeng [4], Arianna Di Lorenzo [4], Seyed Fazel Nabavi [5], Kasi Pandima Devi [6], Seyed Mohammad Nabavi [5]*

[1] Core Facility lab, Iran University of Medical Sciences, Tehran, Iran

[2] National Nutrition and Food Technology Research Institute, Faculty of Nutrition Science and Food Technology, Shahid Beheshti University of Medical Sciences, Tehran, Iran

[3] Physiology Research Center and Department of Physiology, Faculty of Medicine , Iran University of Medical Sciences, Tehran, Iran

[4] Department of Drug Sciences, Medicinal Chemistry and Pharmaceutical Technology Section, University of Pavia, Via Taramelli 12, 27100 Pavia, Italy

[5]Applied Biotechnology Research Center, Baqiyatallah University of Medical Sciences, Tehran 19395-5487, Iran

[6] Department of Biotechnology, Alagappa University, Karaikudi 630004, Tamil Nadu, India

Correspondence to: Applied Biotechnology Research Center, Baqiyatallah University of Medical Sciences, Tehran, P.O. Box 19395-5487, Iran; Tel/fax: +98 21 88617712; E-mail: Nabavi208@gmail.com; Department of Drug Sciences, Medicinal Chemistry and Pharmaceutical Technology Section, University of Pavia, Via Taramelli 12, 27100 Pavia, Italy. Tel.: +39 0382 987388; fax: +39 0382422975. E-mail address: maria.daglia@unipv.it

# Equal contribution.

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Abstract

Over the course of the last three decades, a large body of evidence has shown that polyphenols, the secondary metabolites occurring in plant foods and beverages, exert protective effects due to their antioxidant activity mediated through different mechanisms ranging from direct radical scavenging and metal chelating activities, to the capacity to inhibit pro-oxidant enzymes and to target specific cell-signalling pathways. In the last decade, dietary components, and polyphenols in particular have gained considerable attention as chemopreventive agents against different types of cancer. The signal transducers and activators of transcription (STAT) family is a group of cytoplasmic transcription factors which interact with specific sequences of DNA, inducing the expression of specific genes which in turn give rise to adaptive and highly specific biological responses. Growing evidence suggests that, of the seven STAT members identified, STAT3 is over-expressed in many human tumors (i.e. solid tumors and hematological malignancies) promoting the onset and development of cancer in humans by inhibiting apoptosis or by inducing cell proliferation, angiogenesis, invasion, and metastasis. This review article aims to assess the most recent studies on the role of STATs, with focus on STAT3, in oncogenesis, and the promising effects of some polyphenols on STAT expression. Moreover, the mechanisms behind the anti-inflammatory and antioxidant activities of polyphenols which have an influence on STAT expression are discussed, with a focus on their ability to target specific cell-signalling pathways.

Keywords: Anti-inflammatory response; Antioxidant defense; Cell-signalling pathways; signal transducers and activators of transcription (STAT); Polyphenols

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1. Introduction

Polyphenols are plant secondary metabolites, having an important role in the defense of plants against biotic (i.e. plant pathogens and herbivore animal aggression) and abiotic (e.g. rainfall, aridity, and ultraviolet radiation) stress conditions. Several thousand polyphenols have been identified in higher plants to date. They are generally classified into various subgroups based on variations in their chemical structure, consisting of two or more hydroxyl groups bonded directly to an aromatic ring. These groups are nonflavonoids (i.e. stilbenes, phenolic acids, and lignans) and flavonoids (subdivided into flavonols, flavones, flavanones, anthocyanidins, flavanols, and isoflavones). Over the course of the past three decades, a range of sources have shown that the health protective effects ascribed to polyphenols could be attributed to their antioxidant activity, mediated through different mechanisms of action ranging from direct radical scavenging and metal chelating activities, to the capacity for inhibiting pro-oxidant enzymes (cyclooxygenase and lipoxygenase). In more recent years, polyphenols have been shown to target specific cell-signalling pathways, contributing to an explanation of their functional properties, despite the issue of low bioavailability. The dietary advice given for maintaining proper health is that, at least five portions of fruit and vegetables is to be consumed each day, each consisting of at least 80 grams. The health benefits of many foods are attributed to polyphenols, since these are found more abundantly in many varieties of fruit and vegetables. Though the concentrations at which polyphenols have been found to show activity *in vitro* and *in vivo* are debatably higher than the amounts present in the human diet, the major factor which is to be considered for human consumption is not the raw amount of polyphenols present in the foods or food supplements, but rather their bioavailability, which is the deciding factor for the concentrations of the compound present in the target tissue, and thus available for mediating its effect [1]. On this topic, a recent review was published by McClements et al. which propose the Nutraceutica Bioavailability Classification Scheme (NuBACS) an important tool to evaluate the oral bioavailability of food components with physiological or pharmacological properties, including polyphenols. NuBACS will be used in this review to evaluate if polyphenol concentrations used *in vitro* studies and doses used in *vivo*

(experimental animal) fall within a physiological range [2]. Polyphenols have shown many pharmacological properties including chemoprotective effects against certain forms of cancer [3-5]. Many polyphenols have indeed been shown to modulate the cellular processes involved in tumor initiation and progression (i.e proliferation, survival, inflammation, invasion, metastasis, and angiogenesis). Cancer has a multifactorial pathology, the etiology of which has a 5% to 10% link to inherited genetic aberrations and a 90% to 95% association with acquired genetic mutations due to influences including physical (e.g. UV/solar, ionizing radiations), chemical (pesticides, mycotoxins, environmental pollutants, drugs), and biological (viral such as HBV, EBV, HCV, HIV1, HPV, bacterial such as *H. pylori*, and parasitic such as schistosoma) agents [6]. In the last two decades, a large body of evidence has shown that chronic inflammation leads to the initiation of cancer through a variety of mediators, including cytokines, chemokines, and enzymes, which create an inflammatory microenvironment [7, 8]. In this microenviroment, macrophages and leukocytes induce the production of reactive oxygen or reactive nitrogen species (ROS and RNS). ROS and RNS do play a protective role, but over time their presence leads to severe oxidative stress with associated deleterious effects, such as the production of mutagenic agents (i.e. peroxynitrite) which react with DNA to induce mutations and cause overexpression of cytokines which promote inflammation, such as tumor necrosis factor-α (TNF-α), which induce chronic inflammation [9].

Studies have shown that signaling pathways mediated by cytoplasmic transcription factors including NF-κB, β-catenin, NOTCH and STATs, play a major role in modulating apoptosis in cancer cells [10]. The STAT family, of Signal Transducers and Activators of Transcription, are cytoplasmic transcription factors which migrate from the cytosol into the cell nucleus when activated, where these STATs can interact with specific sequences of DNA, inducing the expression of specific genes which in turn give rise to adaptive and highly specific biological responses [10, 11]. STATs are latent transcription factors which regulate cellular signalling in response to many pro-oncogenics such as cytokines [12], oncogenes [13], hormones [14] and growth factors [15], when bonded to their corresponding receptors. This group consists of seven members, numbered in order of their discovery,

consisting of STAT1-4, STAT5A and 5B, and STAT6 [16]. These dual-function proteins regulate gene transcription and signal transduction [17]. In humans, STAT genes are located on three seperate chromosomes. STAT1 and STAT4 are located on chromosome 2. STAT3 and both STAT5s are mapped to chromosome 17, whereas STAT2 and STAT6 are clustered on chromosome 12 [18]. Of these different forms, immune repose is regulated by STAT 2, 4 and 6 and the different physiological functions such as control of cell cycle, cell survival and angiogenesis are regulated by STAT1, 3 and 5 [19]. Growing evidence suggests that of the seven STAT members, STAT3 is over-expressed in many human tumors, including solid tumors (lung, gastric, hepatocellular, colorectal and prostate cancers), and hematological malignancies (myeloma, leukemias, and lymphomas). Several studies have shown that STAT3 encourages the formation and development of cancer in humans, inhibiting programmed cell death and inducing proliferation, angiogenesis, invasion, and metastasis of cancer cells [20-22]. This review article aims to evaluate the most current studies on the role of STATs, with focus on STAT3, in oncogenesis and the effects of some polyphenols on STAT3 expression. Moreover, the mechanisms behind the anti-inflammatory and antioxidant activities of those polyphenols which influence STAT3 expression are discussed, with a focus on their ability to target specific cell-signalling pathways. This latter focus has been added to underline the complex mechanisms of action at the basis of the protective activity of polyphenols.

2. STAT3 signalling in human diseases

STAT3 clearly takes a pivotal role in different diseases [23-27]. Dysregulation of STAT3 and related pathways in a pathological environment may affect cell fate, and their targeting can thus improve clinical outcomes [28, 29]. STAT3 is a pleiotropic agent that participates in the control of astrocyte reactivity (which is characterized by changes in the transcriptional and functional changes of astrocytes, including over expression of filament proteins), in a JAK-dependent fashion[30]. Likewise, the activity of STAT3 in oligodendroglial cells (a type of neuroglial cells found in the CNS) is

indispensable for developmental CNS myelination and myelin repair [31]. Many existing studies indicate that under neurodegenerative conditions, activation of JAK2/STAT3 by therapeutic agents decreases pro-inflammatory cytokines and increases the expression of anti-apoptotic factors that in turn confer neural survival, whereas other findings claim that JAK/STAT inhibitors may inhibit microglial activation and repress innate and adaptive immune responses to protein aggregates [32-35]. In a study by Huang and coworkers, STAT3 inhibition resulted in protection of retinal ganglion cells against ischemia through suppression of astrogliosis and astrocyte reactivation in the optic nerve [36]. During neurodegeneration, depletion of neurofilaments increase the activation of STAT3 via phosphorylation at Y705 and subsequently the STAT3–stathmin interaction contributes to stabilization and dynamics of microtubules and restores axon elongation [37]. Besides, dysregulation of STAT3 has been observed in cardiovascular diseases [38]. During cardiovascular disease, activation of STAT3 leads to recruitment of inflammatory cells to the vessel wall and formation of lesions. STAT3 activators inhibit adverse cardiac remodeling in subacute phase of myocardial infarction and decrease the onset of chronic heart failure [39]. Moreover, mTOR inhibitors protect the diabetic heart, allowing it to cope with reperfusion injury via STAT3 activation [40]. STAT3 is associated with obesity, and its inhibition decreases obesity-induced thyroid carcinogenesis in animal models [41, 42]. Obesity enhances resistance to anti-VEGF therapy in breast cancer through a STAT 3-related mechanism, which contributes to the overexpression of FGF-2 factor. STAT3 inhibitors may prevent obesity and improve depressive symptoms related to obesity [43]. It has also been found that that pro-inflammatory cytokines may hamper the spermatogenesis process through a STAT3-dependent mechanism [44]. In macrophages, the IL-10 pathway has a central role in the pathology of polycystic kidney disease, and its activation is associated with the STAT3 pathway [45]. STAT3 is an important regulator of the myofibroblast cytoskeleton and pulmonary fibrosis [46]. Angiotensin converting enzyme deficiency affects MMP (matrix metalloproteinase) activation and STAT3 phosphorylation signaling, which contribute to the onset of inflammatory responses in lung injury [47]. STAT3 inhibitors have also been observed to exert a protective effect against LPS-induced acute lung injury [48, 49].

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3. STAT3 signalling in cancer

STAT3 solves an important function in numerous cellular processes including metabolism [50], angiogenesis [51], immunity [52], motility [53], apoptosis [54] and cell differentiation [55]. Recent evidence suggests that in addition to STAT3, STAT5 and STAT6 also play a significant role in tumorigenesis [56]. However, STAT3 acts as a nuclear factor in the oncogenic signalling pathways and acts as a prognostic biomarker in different tumors including melanoma [57], brain [58], head and neck [59], breast [60], acute lymphoblastic leukemia [61], ovarian [62], renal [63], bladder [12], prostate [64, 65], pancreas [66], and colon [67] cancers.

The activation of STAT3 is rapid and transient under normal conditions, whereas STAT3 phophorylation constitutively increases in metastatic melanoma cells [68]. It has a key function in sequential stages of metastasis including invasion, migration, adhesion, infiltration, and colonization [69]. Under pathological conditions (such as human colorectal cancer), the Leukemia inhibitory factor (LIF) activates STAT3 which in turn leads to the overexpression of inhibitor of DNA-binding 1 (ID1), increasing MDM2 expression and resulting in p53 protein degradation [70].

The inactive form of STAT3 is monomeric, while the active form is a dimer. Under pathological conditions, STAT3 regulates gene transcription through phosphorylation at tyrosine 705 or serine 727 sites, dimerization and translocation into the nucleus [71]. Phosphorylation of mitochondrial STAT3 (p-STAT3) at serine 727 site modulates mitochondrial respiratory activity [72]. In addition, a recent investigation reported that unphosphorylated STAT3 is an important regulator in the organization of chromatin, whereas acetylated STAT3 contributes to DNA methylation which leads to the silencing of tumor-suppressor genes [73]. Nucleophosmin (NPM) is a shuttle that facilitates translocation of p-STAT3 from cytoplasm to the nucleus. Nucleophosmin holds a key role in cell survival and is dramatically overexpressed in the majority of melanoma cell lines [74].

Phosphorylated STAT3 increases gene transcription after entering the nucleus and binding to STAT-specific DNA motifs. STAT3 activation increases the expression of anti-apoptotic proteins after

the binding of p- STAT3 to the corresponding DNA in the nucleus. Reciprocal phosphotyrosyl-SH2 domain interactions lead to STAT3 dimerization [75]. Janus kinase 2 (JAK2)/STAT3 is an intrinsic pathway active in cancer cells, which accounts for inflammation in melanoma [76]. STAT3 is associated with JAK2/JAK1, and targeting JAK2/STAT3 signalling with anticancer drugs inhibits the growth of cancer cells [77]. JAK proteins are directly associated with transmembrane receptors. Some ligands such as cytokines can constitutively attach to receptors in melanoma cells and increase the catalytic activity of JAK proteins. JAK proteins indirectly phosphorylate STAT3 at the tyrosine 705 position [78].

In addition, STAT3 plays a crucial role in cell proliferation in certain cancer cells, by the promotion of G1/S and G2/M transitions through cyclin D1, cyclin B and CDK1 stimulation [79]. It has been reported that activated STAT3 increases the expression of antiapoptic proteins, resulting in survival and tumorigenesis [80]. Moreover, p-STAT3 downregulates the p53 tumor suppressor gene, which can in turn indirectly, suppress the expression of pro-apoptotic genes [81].

4. STAT3 signaling in cancer inflammation

Both clinical and epidemiological studies have suggested a strong association between cancer and inflammation. How inflammation promotes cancer growth is still not clearly understood, however transcription factors like NF-κB and STAT3 are believed to be the major factors linking inflammation and cancer [82]. Cytokines, which are recognized as important mediators linking inflammation and cancer, are induced by STAT3 activation leading to inflammatory responses. Some oncogenes and cytokines, such as IL-5 [83], IL-6 [84], IL-9 [85], IL-10 [86], IL-11 [87], IL-22 [88], IL-25 [89] and oncostatin M [90], activate STAT3. IL-22 is important regulator of epithelial regeneration in intestinal stem cells that induces STAT3 phosphorylation and cell growth [91]. IL-11 induces STAT3 phosphorylation in some cells, such as colorectal ones, during both differentiation processes and pathological conditions, consequently contributing to differentiation or cancer progression [92].

Activation of STAT3 under pathological conditions causes overexpression of many genes [18], including expression of the protein matrix metalloproteinase 2 (MMP2) which, through a very complex cascade effect, leads to cell invasion and metastasis of ovarian cancer cells [93]. The MMPs are zinc-dependent endopeptidases which modulate inflammation through regulation of the activity of cytokines, chemokines and growth factors [94]. Excessive phosphorylated STAT3 encourages vascular endothelial growth factor (VEGF) expression which plays a part in angiogenesis in tumor cells [95]. VEGF is a chemokine which acts as a signaling peptide in aiding tumour growth, further leading to metastasis [96]. Tyrosine kinases such as SRC kinases, JAK kinases and growth factor receptors (with intrinsic tyrosine-kinase activity) are continuously activated in cancer cells and act as STAT3 activators [97]. IL-6 is a mediator for the JAK-STAT3-VEGF-C signal pathway, which promotes the growth, invasion and lymph angiogenesis of gastric cancer [98]. Experimental metastasis assays display a strong association between p- STAT3 content and the adhesion of human melanoma cells to blood vessels for the invasion of other body organs [99]. In addition, some intracellular pathways affect JAK–STAT3 signaling in malignancies, including Toll-like receptors (TLRs), Gprotein-coupled receptors (GPCRs) and microRNAs. GPCRs consist of a family of membrane proteins which transmit signals from the extracellular space to the cytoplasm. JAKs and STATs are proteins downstream of GPCRs which activate STAT3 in the tyrosine 705 site. During antibody production and IL-10 secretion, TLR activate STAT3 in B cells [73].

5. Oxidative stress driven STAT3 activation

A growing body of evidence highlights the link between cancer development and chronic inflammation, which in turn are both caused by oxidative stress, which can be considered to be excessive ROS and RNS generation, with respect to their elimination. Under physiological conditions, cell metabolism yields ROS and RNS, which can be considered to be by-products of the cellular redox processes. They play a dual role, depending on their concentration. At low or moderate concentrations, ROS and RNS are beneficial for physiological functions of the immune system and for maintaining

cell proliferation, host defense, signal transduction and gene expression. At high concentrations, free radicals damage DNA, attaching to nitrogenous bases and the sugar phosphate backbone. They damage proteins, inducing the oxidation of amino acids and prosthetic groups and causing the cross-links and protein aggregates, and damage lipids with the generation of peroxides. In turn, biomolecule oxidative damage increases ROS and RNS production, leading to a vicious circle [100, 101].

It has been observed from recent studies that oxidative stress induces apoptosis through both mitochondria dependent and independent pathways [102]. It is interesting to observe that STAT3 acts as an important regulator of survival of cells, once the cell is exposed to apoptotic signals such as oxidative stress. STAT3 mainly causes the upregulation of Bcl-XL and survivin (the anti-apoptotic proteins) as well as the inactivation of caspases. The oxidative stress mediated activation of STAT3 is through the phosphorylation of STAT3 by a PTK (protein Tyrosine Kinase), specifically SYK (Spleen tyrosine kinase), in lymphoid cells [103]. In human lymphocytes, exposure to the ROS H_2O_2, modulates the tyrosine phosphorylation of STAT3 and activates it, which further leads to the translocation of the STAT3 into the nucleus [104].

6. Antioxidant, anti-inflammatory and STAT3 inhibitory activities of polyphenols: Potential mechanisms of action of their protective effects against cancer

On the whole, oxidative stress, inflammation and cancer have been suggested to be closely related, and oxidative stress and inflammation have also been associated with the activation of STAT3 in cancer [105]. Since STAT3 solves an important function in cancer and its associated inflammation process, polyphenols and other compounds which suppress oxidative stress, inflammation and STAT3 phosphorylation could be considered as useful targets for the treatment of cancer.

6.1. Antioxidant and anti-inflammatory activities of polyphenols

Flavonoids are the most numerous chemical class of phenolic compounds. Many flavonoids are widely distributed throughout all plants, while many others are only found in a select few species of

plants. Quercetin (3,3′,4′,5,7-pentahydroxyflavone) is a flavonol which can be considered to be one of the most widespread polyphenols present throughout the plant kingdom, with the exception of fungi and algae [106]. According to NuBACS [2],the bioavailability of quercetin is low. In fact, it has poor bioaccessibility, being trapped in plant tissues and considering its strong interactions with proteins. Moreover, most quercetin absorbed is extensively metabolized and excreted. Because of its wide distribution, quercetin is also one of the most studied flavonoids. Many studies have reported the protective activity of quercetin against pathologies whose major causes of development and progression are considered to be chronic inflammation and oxidative stress. These investigations have been carried out *in vitro*, as well as in animals and humans, and have provided a wide range of evidence for the cardio- and neuroprotective effects of quercetin, as well as its positive effects on some forms of cancer. The protective effects of quercetin can be ascribed, at least in part, to antioxidant and anti-inflammatory activities. In fact, quercetin was found to be able to scavenge ROS, including superoxide anion [107], singlet oxygen and lipid peroxy radicals [108], and to chelate iron, maintaining a balanced intercellular labile iron pool level and thus reducing oxidative stress through other means [109].

As far as cardioprotective effects are concerned, several studies have shown that quercetin protects against ROS-induced cardiomyopathy through its radical scavenging activity, through inhibiting the activation of ERK and MAP kinase, and through induction of apoptosis signal transduction pathways [110, 111]. More recently, quercetin was found to reduce doxorubicin-induced cardiotoxicity *in vitro (*H9c2 cardiomyocytes*)* or *in vivo (*C57BL/6 mice*)* by decreasing doxorubicin-induced apoptosis, mitochondrial dysfunction, ROS generation (reduction of malondialdehyde and lactate dehydrogenase levels and increase of SOD activity), reducing DNA double-strand breaks, and up-regulating the expression Bcl-2 (involved in the antiapoptotic effects) and Bmi-1 (involved in the response to DNA damage, mitochondrial function and oxidative stress). These findings encourage potential applications of quercetin in preventing doxorubicin-induced cardiomyopathy [112]. Quercetin also shows neuroprotective effects for various models of neuronal injury and neurodegenerative disease. Besides

antioxidant activity, the mechanism underlying these protective effects could be the activation of Nrf2-ARE [113, 114], a major regulator of cellular defenses against oxidative stress. Moreover, recent investigations have shown that quercetin is connected to the generation and degradation of misfolded protein aggregates occurring in Parkinson's, Huntington's and Alzheimer's diseases as well as amyotrophic lateral sclerosis [115]. Another suggested mechanism for the neuroprotective activity of quercetin is through the induction of the enzyme paraoxonase 2, mainly found in mitochondria, where the presence of antioxidant enzymes is crucial to avoid or reduce oxidative stress [116]. The neuroprotective activity of quercetin could also be ascribed to its anti-inflammatory activity. Bureau et al. [117] showed that quercetin diminishes apoptotic neuronal cell death induced by microglial lipopolysaccharide activation. In addition, quercetin was able to reduce mRNA levels coding for interleukin 1-α and tumor necrosis factor-α. Similar results were reported by an earlier study in which several flavonoids, one of which was quercetin, were found to reduce the expression levels of proinflammatory cytokines and chemokines, suggesting their capacity to protect against neuronal damage induced by neuroinflammation [118].

In addition, quercetin has been studied for its protective activity against cancer. Its effect is mainly ascribed to antioxidant properties. Many studies have been performed on this subject, especially in *in vitro* conditions. Quercetin showed cytotoxic properties targeting many cancerous cell lines (with concentrations between 1 and 40 µM), such as human medullary and papillary thyroid cancer cells (TT and B-CPAP cell lines), liver hepatocellular carcinoma (HepG2), colon carcinoma (Caco-2 and COLO 320 DM9), and gastric cancer cells (NUGC-2, HGC-27, MKN-7 and MKN-28) [119-122]. It was found to be able to induce variations in the distribution of cell cycle phases of different ovarian cancer cell lines resistant to cisplatinum (ovarian carcinoma (SKOV3) and osteosarcoma (U2OS) human cell lines with the cisplatin (CDDP)-resistant counterparts, SKOV3/CDDP and U2OSPt cells) and in human hepatocellular carcinoma cell lines (HA22T/VGH and HepG2 cell lines) [123, 124]. Another recent investigation has shown that quercitrin (quercetin-3-O-rhamnoside) exerts antiproliferative and

apoptotic effects on lung cancer cells (A549 and NCI-H358 cells) in a time and dose dependant manner, by interacting with the immune response [125].

The studies on *in vivo* anticancer activity are more limited than those carried out in *in vitro* conditions, due to the low water solubility and bioavailability of quercetin. One of the most recent *in vivo* investigations studied the effects of quercetin administered through a nanomicelle-based drug delivery system, used to increase its low bioavailability. The results show that this increased the antitumor efficacy of quercetin, reducing the tumor proliferation rate in the PC-3 xenograft mouse model due to the accumulation of quercetin nanomicelles at the tumor site [126].

The mechanisms of action involved in the anticancer activity of quercetin are not completely clear. As well as its cytotoxicity and influence on the cell cycle, some studies have shown that quercetin can inhibit tyrosine kinases involved in the change from non-malignant fibroblasts to sarcoma cells and tumor cell proliferation [127, 128]. Another potential mechanism of action consists in inhibiting mutant p53 protein, found in elevated quantities in the human breast cancer cell line MDA-MB468 [129]. More recently, and investigation found that quercetin activates a caspase cascade (caspase 3 and caspase 9), induces cell cycle arrest, decreases the ratio between the two Bcl proteins (pro-survival, Bcl-XL, and pro-apoptotic, Bcl-XS), inhibits protein kinase B (Akt) which has an important part in a variety of cellular processes, such as apoptosis and cell proliferation, and increases translocation of the apoptosis regulator, Bax, to the mitochondrial membrane [130].

As reported in table 1, which reports the list of studies included in this review, quercetin concentration used in *in vitro* studies ranges from 0.01 µM to 390 µM. According to Phenol-Explorer 3.6, an online database of food polyphenol levels, including *in vivo* metabolism and pharmacokinetics [131], 2 h after ingestion of 200 mg (single dose) quercetin concentration in plasma is 3.54 µM, suggesting that in most of the cited studies the concentrations used are considerably higher than physiological doses and the obtained results do not resemble physiological conditions.

Flavan-3-ols are another class of flavonoids widely distributed throughout the plant kingdom. They occur in berries, aromatic plants (including mint, basil, rosemary, sage and dill), nuts, grapes and wine,

beer (as part of barley and hops), cocoa and tea [106]. Green tea infusions mainly contain epicatechin, epicathechin 3-gallate, epigallocatechin, and epigallocatechin 3-gallate, which undergo oxidation during fermentation and are transformed into thearubigins and then theaflavins. The most attractive and studied compound is epigallocatechin 3-gallate, which is also the most present flavonoid in green tea (about 30% of the dry matter in green tea leaf (*Camellia sinensis* L.)). According to NuBACS [2], epigallocatechin 3-gallate shows poor bioaccessibility, limited absorption, extensive metabolism and high chemical instability, being subjected to auto-oxidation and interaction with metal ions. Epigallocatechin 3-gallate exerts many healthy properties, being able to prevent or control serious chronic conditions including cancers, diabetes, cardiovascular and neurodegenerative diseases, and kidney or liver injury [132-137].

For tea in general, and epigallocatechin-3-gallate in particular, most of literature data from *in vitro* and *in vivo* investigations and clinical trials, supports the anti-cancer activity of epigallocatechin-3-gallate against several forms of cancer, including esophagus, colon, pancreas, liver, prostate, mammary gland cancers and melanoma [138-142]. An increasing number of studies support the theory that oxidative stress mediated by flavanols could have a key involvement in the development of cancer. In fact, epigallocatechin-3-gallate counteracts oxidative stress in a range of cancer cell model systems, but not in normal cells. Murakami et al. showed that tea catechins inhibit lipid peroxidation induced by tert-butylated hydroperoxide in HepG2 cells, decreasing TBARS concentration. Epigallocatechin gallate showed the highest inhibition, followed by epigallocatechin, epicatechin gallate and epicatechin. In addition, tea flavanols exert further protective effects such as the reduction of alpha-tocopherol depletion, the increase of glutathione content, the inhibition of glutathione disulfide (as a marker of oxidative injury) formation, and the activation of glutathione peroxidase [143].

Several studies conducted more recently have achieved similar results. In 2014, Tao et al. Showed that epigallocatechin-3-gallate exerts cytotoxic effects against oral cancer cell lines (SCC-25) and was not active in a HGF-1 human gingival fibroblast model system [144]. This activity was due to the production of ROS, and the subsequent induction of apoptosis. On the contrary, HGF-1 human gingival

fibroblasts yielded lesser effects to an epigallocatechin-3-gallate treatment, indicating that epigallocatechin-3-gallate induces differential effects in oral cancer cells and gingival fibroblasts and could have an inhibitive effect on oral cancer [145].

Another recent study confirmed the results reported above, showing that epigallocatechin-3-gallate only exerts anticancer properties on cancerous cell lines. In fact, this flavanol was found to induce apoptosis, reduce mitochondrial membrane potential, and promote G0/G1 phase cell cycle arrest in hepatocellular cancer cells in humans (HCCLM6 cells) whilst being inactive in non-cancerous liver cells (HL-7702). Regarding the mechanism of action, the effects shown by epigallocatechin-3-gallate were justified by a significant decrease in the expression of B-cell lymphoma 2 **(**Bcl-2, a significant anti-apoptotic protein, one of the oncogenes), and nuclear factor kappa-light-chain-enhancer of activated B cells (NF-κB, a protein complex which regulates DNA transcription, formation of cytokines and cell survival). In addition, the epigallocatechin-3-gallate treatment prompts raised expression levels of Bax (another member of Bcl-2 protein family), p53, caspase-9 and caspase-3 (involved in apoptosis), and the release of cytochrome c. These results show that epigallocatechin-3-gallate manifests cytocidal activity, inhibiting the development of cancer, suggesting potential activity against hepatocellular carcinoma [146].

These results were confirmed by a more recent investigation which reported that epigallocatechin-3-gallate prevents proliferation of cells, and prompts cell cycle arrest and apoptosis in two osteosarcoma cell lines (MG-63 and U-2OS). The mechanism of action underlying these effects appears to be the upregulation of miR-1, a microRNa that solves an important function in the decrease of some cancers in clinical osteosarcoma tumor tissues [147].

In summary, as reported in table 1, the concentrations used in the *in vitro* studies range from 1 µM to 400 µM. According to Phenol-Explorer 3.6 [131], 2 h after ingestion of 200 mg (single dose), epigallocatechin-3-gallate plasma concentration is 0.1 µM. Therefore, the concentrations used in the cited *in vitro* studies are considerably higher than physiological doses.

Unlike widespread flavonols and flavanols, sylibin is a flavonoid that occurs only in the fruit and seed extract (silymarin) of *Silybum marianum* (L.) Gaertn. (also called milk thistle), belonging to the Asteraceae family. Besides sylibin, which occurs as an equimolar mixture of two diastereomers, silymarin contains taxifolin, isosilybin, isosilybin B, silychristin A and silydianin, with other minor components such as silychristin B4 and isosilychristin. The first studies on the chemical composition of milk thistle were conducted in the 1960s. Since then, many hundreds of investigations have been published on its composition, biological and pharmacological properties. Sylimarin has shown *in vivo* antioxidant activity in a number of experimental animal model systems. For instance, in 2006 Mansour et al. showed that in a rat model of cisplatin-induced nephrotoxicity, daily i.p. injections of silymarin (100 mg/kg/day for 5 days) administered one hour prior to an i.p. injection of CDDP (7.5 mg/kg), restored activities of SOD and GSHPx, malondialdehyde (MDA) and nitric oxide (NO) levels, and glutathione content to normality, suggesting that silymarin exerted hepatoprotective properties through its antioxidant activity [148]. More recently, Shaker et al. obtained similar results, showing that a treatment with silymarin (100 mg/kg) in the final 4 weeks of CCl_4-intoxication of Male Wistar rats induced hepatoprotective effects, reducing hepatic fibrosis by about 47% [149]. Silymarin also showed cardioprotective and nefroprotective effects at a dose of 60 mg/kg administered orally for 12 days in doxorubicin induced toxicity male Wistar rats [150]. Moreover, silymarin has been investigated for chemo-preventive activity against some forms of cancer [151, 152]. Silibinin meglumine is a form of this silymarin which is soluble in water, and which serves as an orally active anti-cancer agent by interfering with the epithelial-to-mesenchymal transition (EMT) in EGFR-mutant non-small-cell lung carcinoma cells. Silymarin prompts proteasomal degradation of cyclin D1 by phosphorylating threonine-286 in human colorectal cancer cells [153]. With regards to its mechanism of action, silymarin was found to induce Nrf2 activation. Zhao et al showed that for *in vitro* (in A549 cells) and *in vivo* (in paraquat-induced lung injury male Sprague-Dawley rats) conditions, silymarin upregulates the levels of Nrf2, and thus may be a potential therapeutic drug against lung injury [154]. In addition, another mechanism underlying the protective effects of silymarin could be ascribed to a decrease in

inflammatory response through inhibition of the NF-κB pathway. One of the first investigations showing the inhibitory effect of silymarin on NF-κB activation was published in 1998 by Saliou et al. [155]. Since then, several studies have reported similar results, suggesting that silymarin and its components possess strong anti-inflammatory properties, revealing an emerging mechanism of protective effects for both liver disease and inflammation-based chronic pathologies [156-162].

Despite the wide range of physiological and pharmacological activities of silymarin and its components, silybin is not absorbed well, as is the case with many other polyphenols. In the '90s, many investigations showed that the absorption of silybin can be considered practically nil, and an improvement in silybin bioavailability could be achieved through liposomal silybin [163-165]

The studies reported in this review, in considering free silybin, are limited in drawing conclusions on its bioactive properties, without taking into account its poor bioavailability. Therefore, *in vitro* studies should be performed considering liposomal silybin.

Among non flavonoid polyphenols, one of the most studied is resveratrol (3,5,4'-trihydroxy-trans-stilbene), a molecule based on stilbene with two phenolic rings linked by a styrene double bond (Figure 1). The earliest studies on resveratrol showed its potential protective activity against cardiovascular diseases, demonstrating an *in vitro* anti-aggregating effect on platelet-rich plasma from healthy volunteers, both alone and in association with red wine. Resveratrol also demonstrated endothelium-dependent vasorelaxing activity, which appears to be mediated by the nitric oxide NO-cGMP pathway [166, 167]. Since then, more than one thousand investigations have studied the physiological and pharmacological properties of resveratrol, primarily those relating to its antioxidant activity. One of the first papers on potential antioxidant properties of resveratrol was published by Khanduja et al in 2003. The antiradical activity was determined in both an *in vitro* chemical system (DPPH assay), and in a biological model system against peroxide radicals, whose formation was induced by t-butylhydroperoxide in hepatic and pulmonary homogenates [168]. More recent studies have focused on the ability of resveratrol to improve oxidative stress. Chen et al. showed that resveratrol induces the overexpression of antioxidant enzymes (i.e. heme oxygenase 1) through

transcriptor factor Nuclear factor erythroid 2-related factor 2 (Nrf2) [169]. In a murine model system resveratrol was found to upregulate the expression of Nrf2 and glutathione, and increase the activities of antioxidant enzymes (catalase, heme oxygenase-1, and superoxide dismutase) reducing malondialdehyde, a lipid peroxidation marker [170]. As far as its anticancer activity is concerned, resveratrol has been shown to modulate multiple cellular pathways relevant to tumorigenesis and acts as a pleiotropic substance, involving signalling pathways related to extracellular growth factors, cell proliferation, apoptosis inflammation, the immune system, and genome instability [171-177].

Moreover, many investigations have shown that resveratrol counteracts multidrug resistance and could have a promising role in adjuvant therapy, associated with synthetic chemotherapy agents (i.e 5-fluoruracil, doxorubicin, cisplatin, and metformin) [178-181].

According to NuBACS [2], resveratrol shows low bioaccessibility because of a high affinity for proteins and interactions with fatty acids [182, 183]. Moreover, resveratrol shows rapid absorption which is unfortunately counterbalanced by the action of efflux transporters embedded within epithelium cell membranes, which transport resveratrol back into the intestinal lumen, and the first hepatic step, which allows for little free resveratrol, reducing its plasma concentration. In addition, resveratrol is highly degraded by oxidative reactions and is submitted to extensive metabolism that induces rapid excretion. Thus, human studies on resveratrol bioavailability unanimously show that it is difficult to detect resveratrol in plasma even following the consumption of doses higher than those found in foods or food supplements [184-186].

In the reported *in vitro* studies, resveratrol has been tested in concentrations between 1 µM and 50 µM (table 2), definitely higher than those found in plasma after resveratrol consumption. In summary, similarly to many other polyphenols, resveratrol low bioavailability is a factor that decreases its *in vivo* efficacy. So the results obtained from *in vitro* studies performed at non physiological concentrations, must be interpreted with caution when trying to extrapolate its effect in *in vivo* studies [187].

Another widely consumed non-flavonoid polyphenol, curcumin (1,7-bis(4-hydroxy-3-methoxyphenyl)-1,6-heptadiene-3,5-dione), is the principal natural polyphenol in the rhizome of *Curcuma longa* L. (turmeric), which has been traditionally used in Asian countries as a herbal remedy for its anti-oxidant, anti-inflammatory, and anti-microbial effects [188]. According to NuBACS, curcumin shows poor bioavailability [2]. In fact, its bioaccessibility is very low, particularly due to its low solubility in gastrointestinal fluids and low stability under alkaline pH and oxygen. In addition, curcumin has limited intestinal uptake and rapid metabolism, leading to extensive glucuronidation and sulfation. All these factors are responsible for the concentration at nanomolar levels found in human plasma [189].

Early studies showed that this polyphenol exerts its antioxidant activity through antiradical properties against ROS [190]. Subsequent research has shown that curcumin can interfere with oxidative stress and inflammation through suppression of pro-oxidant pathways such as the Kelch ECH associating protein 1and nuclear factor erythroid 2-related factor 2 (Keap1-Nrf2) pathway, which acts as the main moderator of cytoprotective reactions to endogenous and exogenous stress from ROS [191]. A recent investigation has shown that curcumin induces an overexpression of Nrf2 and then increases the action of phase-II antioxidant enzymes (i.e. glutathione-S-transferase, glutathione reductase, and NAD(P)H: quinine oxidoreductase 1), and modulates mediators of inflammation such as iNOS and COX2 in liver of mice with lymphomas [192]. Moreover, curcumin suppresses the overexpression of inflammatory mediators (Monocyte Chemoattractant Protein-1 (MCP-1) and TNF-alpha) in in vitro conditions (on vascular smooth muscle cells) through inhibition of TLR4, MAPK, and NF-κB pathways, by inhibiting intracellular production of ROS mediated by NADPH [193]. The antioxidant and anti-inflammatory nature of curcumin is considered to be the basis of its anticancer activity. In 1985, Kuttan et al. showed that turmeric possessed cytotoxic activity *in vitro* (Chinese Hamster Ovary (CHO) cells, lymphocytes and Dalton's lymphoma cells) and reduced the development of animal tumors *in vivo* (a murine model system) [194]. Many experimental animal studies and clinical trials have studied the capacity of curcumin to act as both an anticancer agent and as an

adjuvant in anti-tumour therapies. Curcumin was found to protect against cancer by restoring the expression of caspase [195], exerting influence on tumour suppressor p53 [196], and inducing cell cycle arrest [197]. Moreover, many clinical trials have focused on its ability to reduce adverse effects associated with cancer treatments [198-200] yielding interesting results which advocate further clinical trials on curcumin targeting a variety of cancer conditions.

In summary, in the cited *in vitro* studies, curcumin was studied in concentrations between 5 µM and 27 mM (table 2), whilst in human plasma it is found at nanomolar levels, suggesting that the reported results do not resemble physiological conditions.The phenolic alcohols, such as tyrosol and hydroxytyrosol, are another class of polyphenols with several biological functions. These phenolic compounds occur naturally in extra virgin olive oil, which also contains other polyphenols in minor concentrations (i.e. flavonol glycosides which include luteolin 7-*O*-glucoside, apigenin 7-*O*-glucoside, rutin, anthocyanins, cyanidin 3-*O*-glucoside and cyanidin 3-*O*-rutinoside, secoiroidoids such as oleuropein) [201, 202]. The phenols present in extra virgin olive oil are responsible for its long shelf-life, several sensorial properties (such as its bitter, astringent, pungent, throat-catching taste and color) and its protective effects against cardiovascular and neurodegenerative pathologies, metabolic syndrome, and cancer. Its cardiological properties include vasodilatatory and anti-platelet aggregation effects, as well as the improvement of processes related to thrombogenesis and brain ischemia [203-205]. As far as neuroprotection is concerned, olive oil phenolic compounds interfere with aggregation of amyloid beta peptide (Aβ) and Tau protein [206-208]. With regards to metabolic syndrome, olive oil polyphenols attenuate alterations to the metabolism, including concentrations of glucose in plasma, triglyceride and total cholesterol concentrations [209]. Moreover, its potential anticancer properties are ascribed to its effects on pro- and anti-oncogenic signalling pathways, which increase cell apoptosis and thus decrease cell proliferation [210-212].

Most of the beneficial activity of olive oil has been linked to its high proportion of monounsaturated fatty acids (85% oileic acid) and are linked to the antioxidant and antinflammatory activities of polyphenolic compounds, which modulate the function of several genes [213]. The first

studies on hydroxityrosol were focused on its ability to prevent LDL oxidation [214], platelet aggregation [203], inhibit pro-xidant enzymes (i.e. lipoxygenases and cyclooxygenase) [215] and exert in vitro antioxidant activity in a number of cell model systems (i.e. erythrocytes, breast (MCF-7 and MDA), prostate (PC3 and LNCap) and colon (HCT116 and SW480) cancer cell lines, Caco-2, and chondrocytes [216-219].

Besides its antioxidant properties, hydroxytyrosol counters inflammation, decreasing generation of nitric oxide, prostaglandin E_2 (PGE_2), cytokines (IL-1 α, IL-1 β, IL-6, IL-12, TNF- α), and chemokines (CXCL10/IP-10, CCL2/MCP-1) in a concentration-dependent manner in Murine macrophages (RAW264.7 cells), in which inflammation was induced by lipopolysaccharide. This suggests a pleiotropic effect on the formation and activity of mediators of inflammation [220].

According to Phenol-Explorer 3.6, hydroxytyrosol concentration in plasma reaches 30 nM 2 h after ingestion of a single dose of 30 ml of virgin olive oil [131]. Conversely, hydroxytyrosol metabolite concentrations are higher, suggesting extensive metabolism of olive oil components. In this case, too, *in vitro* studies, in which the tested concentrations range from 0.1 µM to 400 µM (Table 2), can only give preliminary evaluation of the activity of hydroxytyrosol, which must to be confirmed in *in vivo* studies [221].

6.2. Inhibition of STAT3 signaling by polyphenols

Recent studies have shown that polyphenols can decrease inflammation in inflammatory bowel disease (IBD) and Barrett's esophagus carcinogenesis, by decreasing phosphorylation of STAT3 and STAT1 [222, 223]. Polyphenols have the potential to decrease the mortality of cancer by targeting STAT3 signalling pathways, thus acting as effective drugs for the treatment of malignancies.

Epigallocatechin-3-gallate (EGCG), a flavonoid present in green tea, prevents the onset and development of keloid tumors by targeting the STAT3 signalling pathway. Dephosphorylation of STAT3 by epigallocatechin-3-Gallate decreases collagen production and consequently inhibits tumor

cell growth [224]. Effect of EGCG in cisplatin resistant human tongue squamous cell carcinoma cell line CAL27 revealed that EGCG treatment was able to suppress the activity of AKT kinase in a concentration dependent manner, and also downregulate the expression of phosphorylated AKT and STAT3. AKT (v-Akt Murine Thymoma Viral Oncogene) is a kinase that inhibits apoptosis, and blocking of AKT/STAT3 signaling by EGCG hence reveals that it induced apoptotic death and autophagy in cancer cells [225].

An increasing number of recent investigations stress the importance of nutrition and the use of natural botanical compounds in the prevention and treatment of melanoma [226-228]. Four distinct mechanisms for direct targeting of STAT3 by therapeutic agents have been suggested, including i) targeting STAT3 through disruptions in the SH2 domain or dimerization ii) targeting STAT3 through disruptions in the N-terminal domain iii) targeting STAT3 through disruptions in the DNA-binding domain and iv) targeting STAT3 via oligonucleotide inhibition [29]. For example, some polyphenols such as epigallocatechin-3-gallate can bind directly to the SH2 domain of STAT3 and decrease p-STAT3 levels and cancer cell transformation [230]. Some botanical extracts such as sorghum polyphenol bind to the DNA-binding domain of STAT3 and block gene transcription of antiapoptotic genes [231].

During melanoma, the activation of both NF-κB and STAT3 accounts for resistance to chemotherapy and dysfunction in apoptosis. Resveratrol inhibits NF-κβ and STAT3 signalling, which subsequently downregulate the expression of antiapoptotic genes. Resveratrol decreases the expression of cyclin D1/CDK4 and induces expression of downstream genes which inhibit apoptotic signals in B16 melanoma cells [232]. It has been observed that resveratrol suppresses translocation of p-STAT3 from the cytoplasm to the nucleus. Resveratrol also suppresses progression and metastasis of melanoma cells through IL-6 inhibition, which in turn decreases p-STAT3 content [233]. Resveratol was able to reduce the phosphorylation of STAT3 at both Tyr705 and Ser727 sites in the Human Renal cell carcinoma Caki-1 and 786-O. Electrophoretic mobility shift assay revealed that resveratol not only inhibits the phosphorylation of STAT3, but also modulates the nuclear translocation efficiency and

DNA binding ability of STAT3 in the nucleus. Inhibition of STAT3 phosphorylation occurred along with the inhibition of JAK (the enzyme responsible for phosphorylation of STAT3) and activation of PTPε proteins (Protein tyrosine phosphatase), which correlates with the effect of resveratol on STAT3 [234]. Cancer cells like glioblastoma initiating cells (GIC) exhibit a property called as 'stemness' which confers a self renewal ability and the development of resistance to therapeutic drugs. It was observed that inactivation of STAT3 in GIC converts its 'stemness phenotype' to a 'differentiation phenotype' and prevents the intitiation of GIC into a tumour. Treatment of GIC with resveratol inactivated STAT3 by suppressing the phosphorylation of STAT3 at Tyr 705, thus reducing the stemness property of GIC and also increasing its responsiveness to the therapeutic drug temozolomide [235]. Methylthio-derivatives of resveratrol such as 3-Methoxy-40-methylthio-trans-stilbene (3-M-40-MTS) decrease the ability of p-STAT3 to bind to the target sites of DNA in spontaneously immortalized human keratinocyte cells [233]. In addition, resveratrol enhances the radiosensitivity of tumors by decreasing STAT3 phosphorylation through inhibition of IL-6 [58]. On the other hand, some natural polyphenolic compounds, including resveratrol, can act as BRAF inhibitors. These compounds decrease p-STAT3 levels in melanoma cells via BRAF inhibition [236].

The natural polyphenol Rottlerin inhibits ERK protein, causing a reduction in p-STAT3 [237]. Similary Honokiol, the small polyphenolic compound extracted from the bark of the *Magnolia officinalis* tree, possesses anti cancer activity against breast and lung cancer through inhibition of STAT3 phosphorylation. The epidermal growth factor receptor (EGRF) is a growth receptor which activates STAT3 signaling. Honokiol treatment suppressed lung cancer by inhibiting EGFR, which in turn reduced the extression of pSTAT3 [238]. Polyphenon E, which is a green tea extract, inhibits carcinomas by targeting the STAT3 signalling pathway [239]. Myricetin is a polyphenolic compound that inhibits the binding of p-STAT3 to corresponding DNA sites. In addition, myricetin can suppress JAK phosphorylation and subsequently inhibit the transcriptional activity of STAT3 [240].

Curcumin, which is found in *Curcuma longa* plants, has been extensively studied for its anti-cancer activity. It has been found to inhibit tumor cell growth by decreasing p-STAT3 levels in low doses similar to medium and high doses [241]. Curcumin decreases the levels of p- STAT3, which in turn decreases the escape of apoptotic signals by downregulating antiapoptotic genes. Quercetin, a flavonol present in many fruits and vegetables decreases p-STAT3 content in melanoma cells. Quercetin blocks phosphorylation of STAT3 at the tyrosine 705 (Tyr705) site which results in downregulation of STAT3 targeted genes, such as matrix metalloproteinase and antiapoptotic genes [242, 243]. Quercetin also decreases nuclear localization of STAT3 which in turn results in the suppression of STAT3 transcription activity in melanoma cells [244]. In melanoma cells, Silybin suppresses mitogen-activated protein kinase (MEK)-1/2 phosphorylation. Reduced p- MEK1/2 decreases downstream kinase phosphorylation (extracellular signal-regulated kinase (ERK)-1/2). This blockade of ERK1/2 leads to a decrease in p- STAT3 content and arrests the melanoma cell cycle at the G1 phase [245]. Silymarin reduces melanoma progression through inhibition of MEK/RSK signaling pathways. Suppression of MEK/ RSK signaling decreases STAT3 and NFκB activation [246].

The problems encountered with the applications of polyphenols as anti-cancer drugs include their poor bioavailablity. Hence combinations of these bioactive compounds have been used to enhance the anti-cancer effects of the individual compounds at low concentrations, also overcoming the bioavailability problem. Treatment of the cancer LNCaP and MCF-7 cells with a combination of the polyphenols curcumin (4mg/l) + EGCG (40μM) + arctigenin (1μM) decreased the phopshorylation of the STAT3 nd Akt, when compared with the cells treated with the compounds individually. The combination treatment was also able to modulate other associated signaling pathways of STAT3, such as P13K/Akt and NF-κB [247].In addition to the purified compounds, natural extracts containing these compounds have the ability to interfere with the STAT3 signaling. For example, cocoa extract enriched with polyphenolic compounds has been observed to suppress colitis-associated cancer by targeting the NF-κB/IL-6/STAT3 signalling pathway [248]. Activated IL-6 binds to the membrane-bound glycoprotein IL-6 receptor chain (gp130) to induce its dimerization. After receptor chain dimerization,

activated JAK contributes to phosphorylation of gp130 receptor intracellular domains in the tyrosine residue site. Recruited STAT3 proteins then dock with the phosphorylated residues of gp130 via theSH2 domain which in turn leads to STAT3 phosphorylation and angiogenesis [249]. Cocoa polyphenols block the binding of IL-6 to gp130, which results in the inhibition of gp130 dimerization [236]. Red wine extract, enriched with polyphenolic compounds, displays anti-inflammatory action through the suppression of the JAK/STAT signalling pathway [250]. A blueberry preparation which was enriched with polyphenols was able to significantly inhibit the release of IL-6 and phosphorylation of STAT3 and also interfere with P13K/Akt signaling in the cancer cell lines Murine 4T1, human MCF-7 and human MDA-MB-231 cell lines. The inhibitory effect on STAT3 was accompanied with the modification of MAPK family enzymes, which reveals that the anti cancer effect of polyphenolic extract is mediated through a cross-talk between MAPK cascade and STAT3 pathways [251].

Role of polyphenols in alteration of the other STAT subtypes

The STAT1 protein plays an important role in providing immunity against infectious agents and, with reference to cancer, STAT1 has both good and bad faces acting as both a tumor suppressor and promoter. As a promoter, STAT1 induces an immunosuppressive tumour environment and confers therapy resistance to cancer cells. Since STAT1 abundance was observed in certain tumor types, the effects of polyphenols as STAT1 inhibitors have been studied for cancer therapy [252]. UV radiation, which causes skin carcinogenesis, induces various signaling cascades inside the cell. All three spectra of UV (UV A,B and C) phosphorylate the STAT1 at Ser727 through various kinases. Theaflavins and EGCG, which are the polyphenols present in tea, inhibit the UVB induced Ser 727 phosphorylation of STAT1 and protect against skin carcinogenesis, possibly by blocking the kinases ERK (Extracellular signal regulated kinase), JNK (Jun amino-terminal kinases), PDK1 (Pyruvate dehydrogenase kinase) and p90RSK (Phospho-p90RSK) [241]. The polyphenols EGCG also prevents the

cancer cells from escaping the immune system, which is usually done by the expression of the immunomodulatory protein indoleamide 2,3-dioxygenase (IDO) by the cancer cells. Treatment of Human oral squamous carcinoma cell line HSC-3 with EGCG inhibited the translocation of STAT 1 into the nucleus and caused a downregulation of IDO in Interferon-γ induced cancer cells. EGCG mediates its effect as a cancer immunotherapy agent by blocking the JAK-PKC-δ-STAT1 pathway [242].

Simiar to STAT3, STAT5 is also constitutively active in various types of human cancer and inhibits apoptosis by biding to the promotors of cyclin D1 (cell cycle regulator) and bcl-xL (apoptosis inhibitor). Resveratol treatment in renal carcinoma cells suppressed the phosphorylation of STAT5 at 694/699 Tyr residues. Since phosphorylation of STAT5 is essential for cancer cell proliferation, the inhibition of STAT5 by resveratol could help due to its therapeutic effect against renal carcinoma. The expression of the STAT5 regulated genes which control angiogenesis, cell proliferation, cell cycle regulation and anti-apoptosis was also observed to be suppressed during resveratol treatment, which shows that it facilitates apoptosis in the cells [243].

Certain polyphenols, though they inhibit the phosphorylation of STAT3, exhibit a different effect towards other STAT subtypes. For instance, curcumin inhibited STAT3 phosphorylation in U266 multiple myeloma cells, which is a type of hematologic cancer. However under the same treatment conditions, curcumin did not alter the expression of STAT5 or the level of pSTAT5. Since U266 cells do not express phosphorylated STAT1, the cells were pre-treated with INF-α (to induce STAT1 phosphorylation) and then treated with curcumin, and it was observed that curcumin was able to suppress the phosphorylation of STAT1 in INF-α induced cells [244].

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8. Conclusions

Polyphenols are plant food and beverage components with protective effects on human health mainly ascribed to their antioxidant activity. Over the course of the last decade, a large body of evidence has shown that polyphenols target specific cell-signalling pathways involved in endogenous antioxidant defenses and anti-inflammatory response. On the basis of the literature data collected in this review, polyphenols exert their activities through many mechanisms of action influencing several cell-signalling pathways such as MAK/Erk, NF-κB, apoptosis, Akt, and JAK/STAT. Moreover, polyphenols control Nrf2, which in turn induces the transcription of many proteins involved in the regulation of anti-oxidant and anti-inflammatory defenses. The main limits of these promising results are due to the fact that in most investigations, the tested polyphenol concentrations are higher than those found in physiological conditions, which represents an important disadvantage of literature data.

As far as JAks and STATs are concerned, they regulate growth, survival, differentiation and pathogen resistance. In particular, STAT3 plays a key role in the cancerogenesis. Recent investigations have shown that STAT3 is inhibited by some polyphenols which may have promising effects on the onset and progression of several forms of cancer, especially melanoma, with negligible adverse effects. Therefore, clinical studies will be required in the future to establish therapeutic uses of polyphenols as an adjuvant therapy targeting cancer. Finally, we suggest some points for further research:

– Studies on the pharmacokinetic and pharmacodynamics of selected polyphenols which are able to inhibit STAT3

- Evaluation of the potential interactions of the selected polyphenols and anticancer drugs;

– Assessment of the dosages of these polyphenols required to exert effective and beneficial influence on various forms of cancer and

– Identification of the interactions between the selected polyphenols and target mechanisms.

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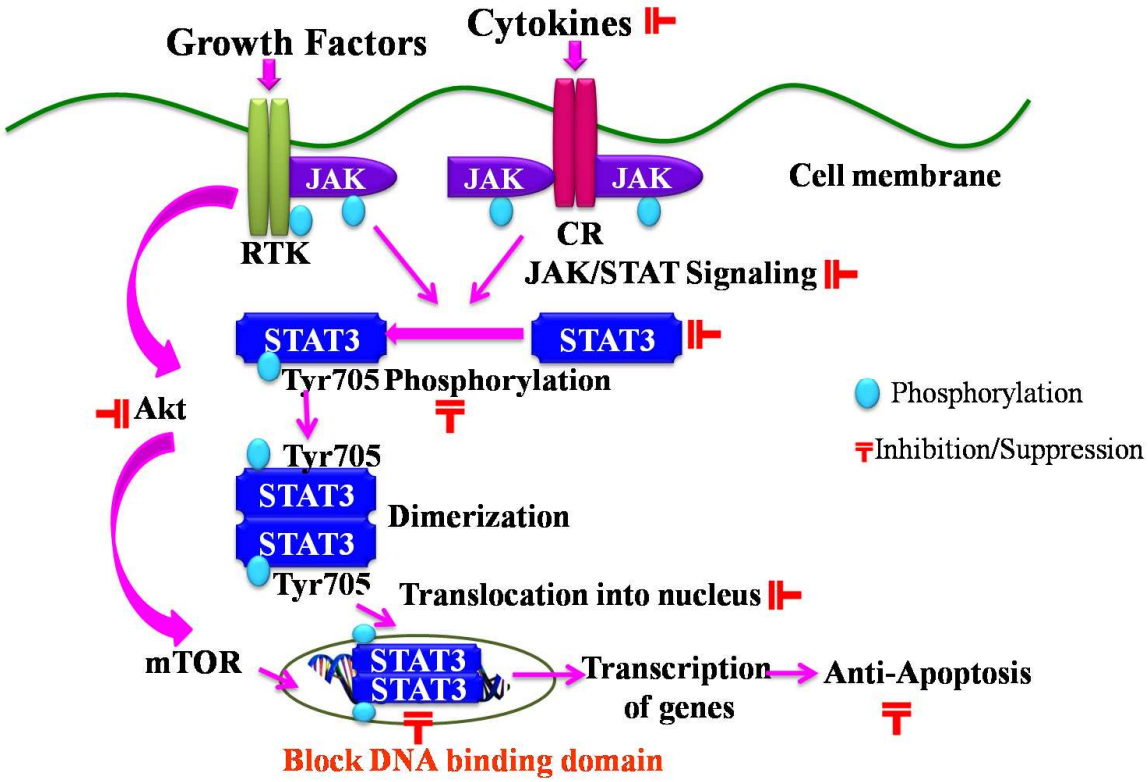

Figure 1. Targeting the STAT3 signaling pathways with polyphenols.

[JAK-Janus kinase; CR-Cytokine receptor; RTK-Receptor tyrosine kinase; STAT3-Signal transducer and activator of transcription 3; Alt-Protein kinase B; Mtor-Mammalian target of rapamycin]

Table 1. List of studies reporting the antioxidant and anti-inflammatory activities of flavonoid polyphenols

Compound/Extract	Activity	Doses	References
Quercetin	Antioxidant	0.01-100 µM (*in vitro*)	[108]
Quercetin	Hepatoprotective effect; ROS quenching activity	100 µmol/L (*in vitro*)	[109]
Quercetin	Radical scavenging activity; Inhibition of ERK and MAP kinase activation; Induction of apoptosis	1-30 µM (*in vitro*)	[110]
Quercetin	Decreasing Bid and p53 expression; Increasing Bcl-2 and Bmi-1 expression; Decreasing mitochondrial dysfunction, ROS generation and DNA double-strand breaks	50-100 µM (*in vitro*) 100 mg/Kg (*in vivo*)	[112]
Quercetin	Neuroprotective effect; Activation of Nrf2-ARE	5-390 µM (*in vitro*) 3.13-100 µM (*in vitro*)	[113]
Quercetin	Increasing total GSH levels and GCLC gene expression;	5-100 µM (*in vitro*)	[114]

	Nrf2 modulation		
Quercetin	Neuroprotection; Induction of enzyme paraoxonasa 2	1-20 µM (*in vitro*)	[116]
Quercetin	Microglia lipopolysaccharide activation; Reduction of IL-1⟨ and TNF-⟨ expression levels	0.1 µM (*in vitro*)	[117]
Quercetin	Reduction of pro-inflammatory cytokines and chemokines expression levels	25-50 µM (*in vitro*)	[118]
Quercetin	Reduction of cytokines production; Anti-inflammatory; Anti-tumor	100-300 µM (*in vitro*)	[119]
Quercetin-3-O-glucoside	Antioxidant activity; Apoptosis induction in cancer cell lines	20-80 µg/mL (*in vitro*)	[120]
Quercetin	Inhibition of the growth of human gastric cancer cells	1-70 µM (*in vitro*)	[121]
Quercetin	Inhibition of hsp70 induction at the level of mRNA accumulation	50-100 µM (*in vitro*)	[122]
Quercetin	Modulation of cycline D1 and B1 levels in cancer cells	10-50 µM (*in vitro*)	[123]

Quercetin	Induction of oxidative stress and cytotoxic effect in human hepatoma cells	40-80 µM (*in vitro*)	[124]
Quercitrin	Increase of caspase-3 activity; Loss of MMP; Apoptotic effect	5-50 µM (*in vitro*)	[125]
Quercetin	Reduction of tumor proliferation rate	0.4-200 µM (*in vitro*) 30 mg/kg (*in vivo*)	[126]
Quercetin	Inhibition of a tumor-coded protein kinase	3-4 µM (*in vitro*)	[127]
Quercetin	Inhibition of p53 mutated protein expression in human breast cancer cell line	5-75 µg/ml (*in vitro*)	[129]
Quercetin	Activation of caspase-3 and -9 cascade; Induction of cell cycle arrest; Decreasing pro-survival and pro-apoptotic protein ratio; Inhibition of protein kinase B; Increasing Bax translocation to mitochondrial membrane	10-100 µmol/L (*in vitro*)	[130]
Epigallocatechin 3-gallate	Inhibition of tumor promotion and chemical carcinogenesis	Different concentration (*in vivo*)	[132]

Epigallocatechin 3-gallate	Preservation of islet structure; Reduction in islet endoplasmic reticulum stress markers	5-20 µM (*ex vivo*) 10 g/kg (*in vivo*)	[133]
Epigallocatechin 3-gallate	Delaying the onset of type 1 diabetes in non-obese diabetic mice; Increasing circulating anti-inflammatory cytokine IL-10 levels	1-10 µM (*in vitro*) 60–90 mg/kg (*in vivo*)	[134]
Epigallocatechin 3-gallate	Improvement of enzymatic and non-enzymatic antioxidant levels; Activation of sirtuin-1, endothelial NO synthase an protein kinase α	100 mg/kg (*in vivo*)	[135]
Green tea extract	Decreasing blood creatinine level	10 ml/kg/day (*in vivo*)	[137]
Epigallocatechin 3-gallate	Inhibition of the growth of malignant esophageal cancer cells; Increasing of caspase-3 expression level; Decreasing VEGF protein level	25-400 µM (*in vitro*) 10 mg/kg (*in vivo*)	[138]

Epigallocatechin 3-gallate	Modulation of Wnt/Hh pathways; Chemopreventive effect	8 µg/kg (*in vivo*)	[139]
Epigallocatechin 3-gallate, theaflavin	Synergistic anticancer activity	2.5-200 µg/ml (*in vitro*)	[140]
Green tea extracts and epigallocatechin 3-gallate	Induction of the $p27^{Kip1}$ CKI; Chemopreventive effects	40-160 µg/ml (*in vitro*)	[141]
Epigallocatechin 3-gallate	Apoptotic effect on cancerous cell; Enhancing expression of c-fos and c-myc genes	40-200 µM (*in vitro*)	[142]
Tea catechins	Reduction of α-tocopherol depletion; Increasing glutathione content; Inhibition of glutathione disulphide; Activation of glutathione peroxidase	2.5-25 µM (*in vitro*)	[143]
Epigallocatechin 3-gallate	Induction of differential expression of genes related to antioxidant defense	0-250 µM (*in vitro*)	[144]
Epigallocatechin 3-	Suppression of SIRT3 mRNA	0-200 µM	[145]

gallate	and protein expression in cancer cells; Increasing SIRT3 activity in normal cells; Modulation of GPx1 and SOD levels	(*in vitro*)	
Epigallocatechin 3-gallate	Decreasing Bcl-2 and NF-┤ B expression in cancer cells; Increase Bax, p53, caspase-9 and -3 expression in cancer cells	0-260 µg/ml (*in vitro*)	[146]
Epigallocatechin 3-gallate	Regulation of miR-1/c-MET interaction	0.0125-0.1 g/L (*in vitro*) 30 mg/kg (*in vivo*)	[147]
Silymarin	Restoring SOD, GPx, GSH activity; Restoring glutathione content, MDA and NO levels	100 mg/kg/day (*in vivo*)	[148]
Silymarin	Hepatoprotective properties; Reduces hepatic fibrosis	100 mg/kg (*in vivo*)	[149]
Silymarin	Cardioprotective effects	60 mg/kg (*in vivo*)	[150]
Silymarin	Inhibitory effect on cancer cell growth; Increasing the binding of	10-75 µg/ml (*in vitro*)	[151]

	Cip1/p21 with CDK2-2 and CDK6; Decreasing of CDK2-, CDK6-, cyclin D1- and cyclin E-associated kinase activity		
Silibinin meglumine	Cancer chemopreventive activity	100 mg/kg (*in vivo*)	[152]
Silymarin	Cancer chemopreventive activity; Increase in cyclin D1 phosphorylation	0-200 μg/ml (*in vitro*)	[153]
Silymarin	Upregulation of Nrf2 levels; Anti-inflammatory and antioxidant activities	200 mg/kg (*in vivo*) 50 μg/ml (*in vitro*)	[154]
Silymarin	Inhibition of NF-κB pathway; Anti-inflammatory activity	0.5-25μg/ml (*in vitro*)	[155]
Silibinin	Inhibition of NF-κB pathway;	0-50 μM (*in vitro*)	[156]
Silibinin	Upregulation of Beclin-1 expression; Increasing p38/p-p38 and NF-κB trasposition	40 μM (*in vitro*)	[157]
Silibinin	Inhibition of NF-κB pathway; Suppression of TNF-⟨, IL-10,	5-50 μM (*in vitro*)	[158]

	TGF-β1, PGE2 and NO production; Anti-inflammatory and anti-fibrotic effects		
Silibinin	Inhibition of TNF-α-induced NF-κB activation; Inhibitory effect on IKKα kinase activity; Chemoprevention	50-200 μM (*in vitro*)	[159]
Silibinin	Decreases TNF-α, IL-6, and IL-8 expression levels; Inhibition of NF-κB pathway	0.05-0.2 mM (*in vitro*)	[160]
Silibinin	Reduction of NF-κB, TNF-α and IL-1®	5-50 μM (*in vitro*)	[161]
Sylmarin	Inhibition of NF-κB pathway	0-50 μg/ml (*in vitro*)	[162]

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Table 2. List of studies reporting the antioxidant and anti-inflammatory activities of non flavonoid polyphenol

Compound/Extract	Activity	Doses	References
Resveratrol	Anti-aggregating activity	2.5-5.0 µg/ml (healty volunteers)	[166]
Resveratrol	Antiradical; Anti-peroxidative activity	12.5-200 µM, 0-1 mM (*in vitro*)	[168]
Resveratrol	Induction of HO-1 expression via Nrf2-ARE signalling; Transient activation of Akt/protein kinase B; Anti-oxidant	15 µM (*in vitro*)	[169]
Resveratrol	Induction of p21waf1and apoptosis	10 µM (*in vitro*)	[171]
Resveratrol	Inhibition of cell proliferation; up-regulation of p21/WAFI expression; Down-regulation of cyclin E, A, -dipendent kinase 2, phosphor-ERK and phospho-p38 expression	10-40 µg/ml (*in vitro*)	[172]
Resveratrol	Down-regulation of E2F family protein expression; Down-	1-25 µM (*in vitro*)	[173]

	regualtion of hyperphosphorylated pRb protein		
Resveratrol	Apoptotic; Induction of Notch1 protein expression; Up-regulation of TTF1, TTF2, Pax8, NIS	10-50 µmol/L (*in vitro*)	[175]
Resveratrol	Chemo-preventive potential	15 µM (*in vitro*)	[178]
Resveratrol	Modulation of autophagic cell death	2.5-40 µM (*in vitro*)	[179]
Resveratrol	Downregualtion of p53/yH2AX/p-chk2	2.5-25 µM (*in vitro*)	[180]
Resveratrol	Decreasing wound healing and clonogenic potential of cancer cells; Inhibition of NF-κB, COX-2, autophagic flux, redox regulation; Induction of apoptosis	IC30 (*in vitro*) 10 mg/kg (*in vivo*)	[181]
Curcuma longa extract	Anti-oxidant; Scavenge DPPH radicals		[190]

Curcumin	Overexpression of Nrf2; Increase of phase II anti-oxidant enzymes; Modulation of inflammatory mediators	50-150 mg/kg (*in vivo*)	[192]
Curcumin	Inhibition of TLR4, MAPK, and NF-κB pathways	5-30 µmol/L (*in vitro*)	[193]
Turmeric extract	Cytotoxic activity; Reduce tumors development	0.02-10 mg/ml (*in vitro*) 10-40 mg/animal (*in vivo*)	[194]
Curcumin	Induces apoptosis; Decreases mitochondrial membrane potential; Activation of caspase-3 and -9; Induce cytochrome c release, increases Bax, and p53; Reduces Bcl-2	0-30 µg/ml (*in vitro*)	[195]
Curcumin	Decreases serum TNF-α levels; Increases p53 expression and apoptosis in tumor tissue	360 mg/thrice a day (patients)	[196]
Curcumin	Induction of cell cycle arrest	0-20 µM (*in vitro*)	[197]
Curcumin (Meriva)	Downregulation of inflammatory pathway; Anti-oxidant activity	Three tablet a day (patients)	[198]

Curcumin	Reduction of TNF-α, TGFβ, IL-6, substance P, MCP-1, hs-CRP, CGRP	180 mg/day (patients)	[200]
Hydroxytyrosol	Inhibition of platelet function and eicosanoid formation	400 µM, 10-1000 mM (*in vitro*)	[203]
Virgin olive oil	Decreases plated aggregation an thromboxane B2; Reduces the decrease in glutathione concentration; Reduction of lactate dehydrogenase activity	0.25-0.5 ml/kg/day (*in vivo*)	[204]
Tyrosol	Reduction of the infarct volume; neuroprotective effect	3-30 mg/kg (*in vivo*)	[205]
Tyrosol Hydroxytyrosol	Prevention of the decrease of GSH induced by H_2O_2 or Aβ; Increase of NF-κB nuclear translocation	50-100 µM (*in vitro*)	[207]
Hydroxytyrosol Oleuropein Oleuropein aglycone	Inhibition of Tau aggregation	0.1-1000 µM (*in vitro*)	[208]
Olive leave extracts	Serum glucose, total cholesterol, triglycerides, urea, uric acid, creatinine, AST and ALT decrease; antidiabetic	0.1-0.5 g/kg (*in vivo*)	[209]

Hydroxytyrosyl acetate	Increases p21 and CCNG2 protein expression; Decreases CNB1 protein expression; Up-regulation of BNIP3, BNIP3L, PDCD4 and ATF3; Activation of caspase-3; Uperegualtion of CYP1A1 and UGT1A10	5-50 µM (*in vitro*)	[210]
Hydroxytyrosol Oleuropein	Inhibition of estrogen-dependent rapid signals	10-75 µM (*in vitro*)	[211]
Olive oil extract	Inhibition of p38 and CREB phosphorylation; Reduction of COX-2 expression	10-100 µg/ml (*in vitro*)	[215]
Hydroxytyrosol	Anti-oxidant	50-200 µM (*in vitro*)	[216]
Hydroxytyrosol	Anti-oxidant; Pro-apoptotic	100 µM (*in vitro*)	[217]
Hydroxytyrosol	Protection of chondrocytes from DNA damage; Induction of SIRT-1; Anti-oxidant	100 µM (*in vitro*)	[219]
Hydroxytyrosol	Inhibition of NO and PGE_2 production; Decrease cytokines and chemokines secrection	0.2-50 µM (*in vitro*)	[220]

Table 3. STAT3 signaling and polyphenols

Compound/Extract	Activity	Doses	References
Epigallocatechin-gallate	STAT3 dephosphorylation and STAT3-signaling pathway inhibition	25-50-100 µM (*in vitro*)	[224]
Epigallocatechin-gallate	Decreasing p-STAT3 proteins levels	0,1-1000 µM (*in vitro*)	[230]
Red wine extract	JAK/STAT targeting	200 – 400 – 600 µg/ml (*in vitro*)	[250]
Sorghum polyphenols	Binding to DNA-binding domain of STAT3, thus blocking gene trascription	10-50 µg/ml (*in vitro*) 1.8 mg/kg (*in vivo*)	[231]
Resveratrol	Inhibition of NF-kB and STAT3 signaling; decrease of cyclin D1/cdk4 expression	0-500 µM (*in vitro*) 12.5 mg/kg (*in vivo*)	[232]
Resveratrol	Suppression of p-STAT3 translocation from cytoplasm to the nucleus; IL-6 inhibition, thus decreasing p-STAT3 content	0-100 µM (*in vitro*)	[233]

Resveratrol	IL-6 inhibition and decrease of STAT3 phosphorylation	0-200 µM (*in vitro*)	[58]
Rottlerin	Inhibition of ERK protein and STAT3 phosphorylation	20 µM (*in vitro*)	[237]
Curcumin	Decreasing p-STAT3 levels	0.5-6.75 µM (*in vitro*) 100 – 200 – 400 mg/kg (*in vivo*)	[241]
Quercetin	Decreasing of p-STAT3 levels Blockage of STAT3 phosphorylation at the Tyr705 site Decreasing nuclear localization of STAT3	40 - 60 - 80 µM (*in vitro*) ----- 2.5-100 µM (*in vitro*) 5 mg/kg/twice a week (*in vivo*)	[242] [243] [244]
Silybin	Suppression of mitogen-activated protein kinase (MEK)-1/2 phosphorylation, decreasing p-STAT3 content in melanoma cells	40 - 80 µM (*in vitro*)	[233]
Sylimarin	Inhibition of MEK/RSK	40 - 80 µM	[245]

	signaling, decreasing STAT3 and NF-kB signaling	(*in vitro*)	

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- ► The STAT3 is known to have a distinct role in cancer progression and development
- ► Extensive evidences shows the promising role of polyphenols on cancer
- ► Could polyphenols exert the anticancer effect by STAT3 regulation?

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Dear Editor

All of coauthors and my department representative are fully aware of this submission and agree with it.

Best regards

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