Abstract: Over the past decades, an increase in the incidence rate of cancer has been witnessed. Although many efforts have been made to manage and treat this life threatening condition, it is still one of the leading causes of death worldwide. Therefore, scientists have attempted to target molecular signaling pathways involved in cancer initiation and metastasis. It has been shown that signal transducers and activator of transcription (STAT) contributes to the progression of cancer cells. This important signaling pathway is associated with a number of biological processes including cell cycle, differentiation, proliferation and apoptosis. It appears that dysregulation of the STAT signaling pathway promotes the migration, viability and malignancy of various tumor cells. Hence, there have been many attempts to target the STAT signaling pathway. However, it seems that currently applied therapeutics may not be able to effectively modulate the STAT signaling pathway and suffer from a variety of drawbacks such as low bioavailability and lack of specific tumor targeting. In the present review, we demonstrate how nanocarriers can be successfully applied for encapsulation of STAT modulators in cancer therapy.

Keywords: nanoparticle; drug delivery; STAT3; cancer therapy; bioavailability

1. Introduction

As a multidisciplinary field, nanotechnology can be extensively applied in medicine, chemistry and engineering [1,2]. Nanotechnology aims to the development of materials and structures with low size (1–1000 nm) [3]. Over the past decades, significant attention has been directed towards nanotechnology for diagnosis and management of cancer [4]. Clinically, application of a number of strategies such as chemotherapy, radiotherapy and surgery seems to be beneficial in the inhibition of tumorigenesis. However, metastasis and subsequent recurrence are the most challenging problems in cancer therapy [5,6]. Accumulating data demonstrates that there are few major drawbacks
associated with conventional cancer therapeutic strategies including the resistance of cancer cells to chemotherapy and radiotherapy, the invasive feature of surgery, unexpected side effects and poor tumor targeting as well as low bioavailability of anti-tumor drugs [7], thereby demanding novel strategies for cancer therapy.

Nanocarriers can be considered as potential candidates in cancer therapy. The low particle size of nanocarriers enables them to effectively penetrate into the blood–brain barrier (BBB) [7]. It appears that application of nanocarriers is associated with enhanced bioavailability of the drug. In fact, nanocarriers can encapsulate the drug to protect it against degradation thus resulting in its enhanced bioavailability for therapeutic application [8]. It is noteworthy that nanoparticles (NPs) provide a minimally invasive-cancer therapy [9] and simultaneously, significantly diminish the chance of resistance and adverse impacts by using a low amount of anti-tumor drug, while the anti-tumor activity is at its highest level [10]. It is possible that mild pH of the tumor microenvironment degrades the drug and more importantly, conventional cancer therapeutic strategies suffer from a lack of specific targeting of cancer cells leading to their toxicity against normal cells. A variety of receptors undergo upregulation in tumor cells and receptor-targeted NPs are of importance in enhancing the delivery of drug into cancer cells [11]. Therefore, based on the high incidence rate of cancer [12], using nanotechnology seems to be a promising approach against this life threatening condition due to its capability in enhancing the anti-tumoral actions of drugs. Currently, various NPs are applied for the delivery of anti-tumor drugs such as solid lipid nanoparticles (SLNs) [13], liposomes [14], niosomes [15], micelles [16], polymeric NPs [17–19], carbon nanostructures [20], viral NPs [21], mesoporous silica NPs [22] and gold NPs [23]. Besides, different methods can be used for drug loading. It has been established that various drugs can be predominantly loaded on nanocarriers by encapsulation, as well as covalent or electrostatic binding [24–28].

Cancer is considered as a malignant condition and deregulation of various oncogenic signaling pathways are generally involved in its progression [29]. For example, Wnt signaling pathway is one of the major signaling cascades that can enhance the proliferation and metastasis of cancer cells [30–32]. On the contrary, nuclear factor erythroid 2-related factor 2 (Nrf2) can also be targeted to overcome resistance of cancer cells to chemotherapy [33]. These studies demonstrate that diverse oncogenic signaling pathways can be effectively modulated to develop novel strategies for cancer therapy [34–37]. In the present review, we describe the various ongoing efforts for delivery of anti-tumor drugs primarily targeting oncogenic STAT3 signaling pathway.

2. STATs Family: Members and Signaling Pathways

The discovery of signal transducers and activator of transcription (STAT) signaling pathway returns back to 1997, when the scientists have found that STATs are involved in mediation of interferon signaling [38]. A variety of hormones, cytokines and growth factors function as upstream modulators of Janus kinase (JAK)/STAT signaling pathway resulting in regulation of important biological mechanisms such as cell cycle, cell differentiation, cell proliferation and apoptosis [39–43]. Besides, the JAK/STAT signaling pathway is involved in complicated mechanisms such as immune regulation and cancer [44,45]. In mammals, there are four genes encoding JAK1, JAK2, JAK3 and TYK2, and seven genes encoding STAT1, STAT2, STAT3, STAT4, STAT 5A and 5B, and STAT6 [46–48]. The expression of JAK3 occurs primarily in hematopoietic cells, while JAK1, JAK2 and TYK2 are ubiquitously expressed [49]. Four major domains are associated with JAKs including N-terminal FERM-domain, SH2-like domain, pseudokinase domain and JH1 domain. It has been demonstrated that FERM and SH2-like domains can contribute to the interaction of JAKs with their receptors [50,51]. On the contrary, STATs effectively affect the transcription of target genes by interaction with DNA regulatory elements (DREs) [52].

Hormones, cytokines and growth factors bind to the receptor leading to the phosphorylation of receptor-associated JAKs. This phosphorylation occurs on the tyrosine (Tyr) residue of JAK that is necessary for stimulation of kinase activity [53]. Importantly, attachment of a ligand to the cell membrane receptor promotes the interaction of receptor-JAK complex to facilitate the phosphorylation
of tyrosine residues of cytoplasmic domains of receptors [54], which can then form docking sites for SH2 domain-containing STAT proteins. Then, phosphorylation of Tyr residues within the C terminal domain of receptor-bound STATs occurs resulting in detachment of STATs from receptors and generation of homo- and heterodimers. The STAT proteins accumulate in the cytoplasm and then, translocate into the nucleus where they bind to the members of gamma-activated sites (GASs) and interferon-stimulated response elements (ISREs) [55–60]. ISREs are limited to interferon (IFN) signaling, while GASs are present at the promoter of genes including acute-phase proteins [61]. It is noteworthy that STAT3 is capable of transferring from the cytoplasm to nucleus and vice versa, regardless of its phosphorylation status [62].

A number of proteins play a significant role in regulation of the JAK/STAT signaling pathway. These characteristic proteins include the suppressor of cytokine signaling (SCOS), protein tyrosine phosphatases (PTP) and protein inhibitors of activated STATs (PIAS) [63]. SCOS proteins suppress JAK/STAT signaling pathway via A) inhibition of JAK phosphorylation, and B) blocking STAT recruitment [64–66]. PIAS proteins prevent the interaction of STAT proteins with DNA. PTP are involved in suppressing JAK proteins [63].

3. Role of STATs in Cancer Hallmarks

Importantly, it has been shown that dysregulation of the STAT signaling pathway is associated with development of a number of pathological conditions, particularly cancer. Notably, it seems that STAT1 is considered as a pro-tumorigenic pathway, so that several studies have revealed that the STAT1 signaling pathway significantly enhances the proliferation and malignancy of cancer cells [9,67,68]. However, there are a variety of studies that demonstrate that down-regulation of STAT1 is related to the enhanced invasion and metastasis of tumor cells [69]. Taking these reports into account, dysregulation of STAT1 (upregulation and down-regulation) occurs in tumor cells. It has been shown that interleukin-6 (IL-6) stimulates the malignancy and proliferation of tumor cells. It appears that STAT2 enhances the proliferation of cancer cells by elevating the level of IL-6/STAT3 [70]. A similar story occurs for STAT3, so that various research studies have confirmed that the STAT3 signaling pathway incredibly increases tumor migration, tumor size and tumor malignancy [71–77]. However, targeting the STAT4 signaling pathway can be considered as a promising strategy in cancer therapy. For example, an upregulation of STAT4 protein can enhance the survival time of patients [78]. Notably, STAT proteins may also act as prognostic signatures in gastric cancer. Moreover, it has been demonstrated that among STAT proteins, STAT4 can determine the prognosis of gastric cancer due to its association with high levels of dendritic cells and CD8+ T cells, whereas STAT3 and STAT6 have minimal prognostic value [79]. Furthermore, miRNA-141-3p inhibits the viability and metastasis of gastric cancer cells through the upregulation of STAT4 [80]. STAT5 and STAT6 contribute in the progression of cancer [41,81,82]. The various members of STAT proteins may also function as upstream modulators of other STAT proteins. STAT5 is an example of this case and it is capable of regulating the expression of STAT3 in tumor cells [83]. Besides, the interaction between STAT proteins may be vital in regulating gene transcription [84]. The STAT signaling pathway can also be involved in the resistance of cancer cells to chemotherapy [85]. For example, accumulating data shows that the RAS signaling pathway may be a key to the malignancy of colorectal cancer (CRC) cells [86,87]. It was found that the interaction between RAS and IFN/STAT signaling pathways [88] can be vital for the induction of the resistance of tumor cells to chemotherapy with trametinib. RAS triggers IFN/STAT signaling pathway by stimulation of STAT1 phosphorylation. Although administration of trametinib is associated with MEK inhibition, the phosphorylation of STAT1 was not found to be affected [89]. IFN/STAT signaling pathway can induce drug resistance in colorectal cancer (CRC) cells via interaction with RAS [89]. Cancer stem cells develop resistance to chemotherapeutic agents by stimulation of the JAK-STAT signaling pathway. Disruption of the JAK-STAT pathway reduces the proliferation and viability capabilities of cancer stem cells [90]. In respect to the potential role of STAT proteins in cancer invasion and metastasis, a number of studies have been performed to elucidate the upstream
modulators of STAT signaling pathway. Long non-coding RNA (lncRNA) PART1 is suggested to be involved in enhancing the malignancy of lung cancer cells via induction of JAK-STAT signaling pathway [43]. MicroRNAs (miRs) are short non-coding RNA molecules, which can affect the invasion of cancer cells due to their role in regulation of important biological processes such as cell differentiation, cell proliferation, cell growth and apoptosis [91–93]. It appears that miR-15a-3p effectively diminishes the malignancy of liver cancer cells by down-regulation of STAT3 [94]. SOCS plays a significant role in induction of immune system [95]. Moreover, in lung cancer, a reduction in SOCS3 enhances the expression of STAT3 thus causing the progression of cancer cells. MiR-410 down-regulation increases the expression of SOCS3 leading to the decreased level of STAT3 protein and minimized progression of lung cancer cells [96]. Notably, application of STAT3 inhibitor is suggested to be beneficial in the treatment of head and neck cancers [97]. These findings highlight this notion that STAT signaling pathway perturbation is involved in various cancers and targeting this pathway using synthetic or naturally occurring drugs is of importance in cancer therapy. Besides, detecting the mediators of the STAT signaling pathway such as lncRNAs and miRs can be beneficial in genetic manipulation. Based on the complexity and dynamic feature of the STAT signaling pathway, providing an effective modulation of the STAT pathway depends on targeting various signaling molecules involved in regulating this multifunctional pathway.

4. STATs Inhibitors

Contemporary therapy is based on targeting the pathways and mechanisms that diseases use. To accomplish this, we should first identify these mechanisms and then create individual molecular drugs that specifically target these pathways. From the theoretical standpoint, targeting one pathway seems very beneficial, but in practice this single therapy is not completely effective and we have not witnessed substantial progress in the eradication of sophisticated pathological disorders, particularly cancer. Besides, using one drug enhances the chance of resistance, so the application of several drugs that affect various molecular pathways diminishes the risk of resistance developing. The targeted therapy of STATs has been advanced due to identification of the unique roles of STATs in various cellular processes. However, over the recent decades, natural and synthetic inhibitors have been developed that can target STAT signaling pathway in various disorders, specifically cancer [98–113]. Among the STAT proteins, there have been many efforts to detect the inhibitors of STAT3, leading to development of more synthetic and naturally occurring inhibitors of STAT3 compared to other STAT proteins. This may be due to this fact that STAT3 and STAT1 proteins are involved in the progression of several tumor cells [114,115]. It can be concluded that STAT3 inhibitors may negatively affect STAT3 signaling pathway via four major actions [116]: i) Inhibition of SH2 domain or dimerization, ii) influencing upstream mediators of STAT3 such as JAK, iii) suppressing STAT3-DNA domain binding, and iv) endogenous modulators of STAT3. However, there are a variety of difficulties that restrict targeting STAT signaling pathway. For instance, it has been demonstrated that there is a similarity among the structures of STAT proteins, leading to reduced specificity in targeting. Moreover, there is a need for more studies to confirm the safety of these inhibitors in clinical trials.

Furthermore, there have been some attempts to interfere with the transcription of genes. However, these strategies suffer from low specificity and a lack of knowledge about appropriate therapeutic doses [117]. Curcumin is a naturally occurring nutraceutical compound with diverse pharmacological impacts such as antioxidant, anti-inflammatory, anti-diabetic and anti-tumor [118–121]. It appears that curcumin is capable of targeting different signaling pathways in stimulation of its anti-tumor activity and JAK-STAT pathway is one of them [122–125]. The induction of apoptotic cell death in H-Ras human mammary epithelial cells is a consequence of direct interaction of curcumin with cysteine (Cys) 259 residue of STAT3. This interaction can lead to the inactivation of STAT3 and subsequently, sensitize tumor cells into apoptotic cell death [126]. Pravastatin is one of the key members of statins with the capability of reducing cholesterol and improving cardiovascular parameters [127]. The
administration of pravastatin has been found to be associated with down-regulation of IFN-γ levels and amelioration of atherosclerosis via reducing the expression of STAT1 phosphorylation [128]. It has been demonstrated that pimozide as a neuroleptic drug is capable of targeting STAT proteins [129]. Pimozide can remarkably diminish the phosphorylation level of STAT5 resulting in high cytotoxicity against K562 cells [130]. As an immunosuppressive compound, leflunomide effectively inhibits IgG1 generation by suppressing tyrosine phosphorylation of JAK3 and STAT6 [131]. Niflumic acid has demonstrated great potential in treatment of asthma by modulation of STAT signaling pathway. It seems that IL-13 is vital in induction of asthma through stimulation of chronic inflammation, eosinophilic infiltration, reversible airway narrowing and airway hyperresponsiveness (AHR) [132–135]. Niflumic acid prevents IL-13-mediated asthma by down-regulation of JAK2 and STAT6 [136]. Cinnamon has a long story in traditional medicine and is extensively used in amelioration of pathological conditions, particularly cancer [137]. The immunomodulatory impact of cinnamon can be attributed to the modulation of STAT proteins, as it suppresses the expression of STAT4 to inhibit the production of IFN-γ [138]. Taking these reports into account, it appears that inhibiting the phosphorylation may be an important strategy for STAT suppression. However, some of them directly bind to the target STAT and suppress its activity. Tables 1 and 2 summarize the selected pharmacological inhibitors of STAT proteins.

### Table 1. Signal transducers and activator of transcription (STAT) inhibitors except STAT3 inhibitors.

| Drug          | Molecular Formula | Target  | Effect                        | Animal Model/Cell Line | Refs     |
|---------------|-------------------|---------|-------------------------------|------------------------|----------|
| —             | 2-(3′,4′,5′-trimethoxybenzoyl)-3-iodoacetamido-6-methoxybenzo[b]furan derivative 1 | STAT5   | Inhibition of STAT5 phosphorylation | K562 cells            | [139]    |
| —             | N’-(4-Oxo-4H-chromen-3-yl)methylene)nicotinohydrazide | STAT5   | Inhibition of STAT5 phosphorylation | Chronic myeloid leukemia (CML) cells | [140]    |
| SEL120-34A   | C_{13}H_{18}Br_{2}C_{2}N_{4} | STAT1, STAT5 | Inhibition of STAT1 S727 and STAT5 S726 phosphorylation | Acute myeloid leukemia (AML) cells | [141]    |
| R763         | —                 | STAT5   | Inhibition of STAT5 phosphorylation | Neoplastic mast cell   | [142]    |
| Pravastatin  | C_{23}H_{36}O_{7} | STAT1   | Prevention of STAT1 expression | Mice                   | [128]    |
| Pimozide     | C_{20}H_{29}F_{2}N_{3}O | STAT5   | Inhibition of STAT5 phosphorylation | K562 cells, peripheral T-cell lymphoma | [130,143] |
| Leflunomide  | C_{12}H_{8}F_{3}N_{2}O_{2} | STAT6   | Inhibition of tyrosine phosphorylation of STAT6 | B cells               | [131]    |
| Niflumic acid| C_{13}H_{8}F_{3}N_{2}O_{2} | JAK2, STAT6 | Blockade of STAT6 phosphorylation | Mouse                 | [136]    |
| Cinnamon     | C_{30}H_{29}O_{19} | STAT4   | Blockade of STAT4 phosphorylation | Mice                  | [138]    |
| Atiprimod    | C_{22}H_{44}N_{2} | STAT3, STAT5 | Inhibition of phosphorylation | AML cells            | [144]    |
Table 2. Natural STAT3 inhibitors.

| Drug                        | Molecular Formula | Effect                                      | Animal Model/Cell Line | Refs |
|-----------------------------|-------------------|---------------------------------------------|------------------------|------|
| Silibinin                   | C_{25}H_{22}O_{10} | Blocking pathways of STAT3 activation       | Endometrial carcinoma cells | [145] |
| Quercetin                   | C_{15}H_{10}O_{7}  | Inhibiting STAT3 signaling pathways         | Lymphoma cells          | [146] |
| Berberine                   | C_{20}H_{18}NO_{4+}| Decrease of STAT3 phosphorylation           | Keratinocytes           | [147] |
| Resveratrol                 | C_{14}H_{12}O_{3}  | Inhibition of STAT3                         | Rat                     | [148] |
| Triterpenes from *Helicteres angustifolia* | —                 | Inhibition of STAT3 phosphorylation         | HT-29 colorectal cancer cells | [149] |
| Butein                      | C_{15}H_{12}O_{3}  | Inhibition of STAT3 expression              | Multiple myeloma cells  | [150] |
| Caffeic acid                | C_{9}H_{8}O_{4}    | Inhibition of activity of STAT3             | Mouse, Human renal carcinoma cells | [151,152] |
| Capsaicin                   | C_{18}H_{27}NO_{3} | Inhibition of STAT3                         | Human multiple myeloma cells | [153] |
| Celastrol                   | C_{29}H_{58}O_{4}  | Inhibition of STAT3 phosphorylation         | Human hepatocellular carcinoma | [154] |
| Cucurbitacin                | C_{32}H_{46}O_{8}  | Inhibition of STAT3 activation              | AML cells               | [155] |
| Diosgenin                   | C_{27}H_{42}O_{3}  | Inhibition of STAT3 phosphorylation         | Human hepatocellular carcinoma cells | [156] |
| Guggulsterone               | C_{21}H_{29}O_{2}  | Inhibition of STAT3 phosphorylation         | Tumor cells             | [157] |
| Honokiol                    | C_{18}H_{16}O_{2}  | Modulation of STAT3 activation              | Breast cancer cells      | [158] |
| Avicin D                    | C_{36}H_{150}NO_{46}| Inhibition of STAT3 phosphorylation        | U266 cells, myeloma cell lines | [159] |
| Piceatannol                 | C_{14}H_{12}O_{4}  | Reduction of P-STAT3 expression             | Mouse                   | [160] |
| Withaferin A analogues      | —                 | Inhibition of STAT3 phosphorylation         | Breast cancer cell line  | [161] |
| Emodin                      | C_{15}H_{10}O_{3}  | Inhibition of STAT3 phosphorylation         | Hepatocellular carcinoma cell lines | [162] |

5. STATs Gene Silencing by RNA Interference

The introduction of the RNA interference (RNAi) mechanism returns back to two decades ago [163]. This phenomenon has resulted in a great advancement in the investigation of the function of RNAs [12]. At this mechanism, small RNAs containing 18–30 nucleotides are designed to act on long RNAs. This action involves stimulation or inhibition of cleavage at the post-transcriptional level [164]. In respect to the modulatory effect of RNAs on STATs, it seems that regulation of RNAs using RNAi is beneficial in the treatment of pathological disorders associated with dysregulation of STAT proteins [165]. Modulation of STAT3 using RNAi is advantageous in treatment of a laryngeal tumor. An animal model was induced to examine the anti-tumor activity. This animal model included immunocompromised mice in that HepG2 cells were transplanted. Suppressing STAT3 protein remarkably diminished the growth rate of tumors. It appears that STAT3 down-regulation is associated with reduced expression of *Bcl-2*, *cyclin D1* and *survivin* genes leading to the stimulation of apoptotic cell death [166]. A similar observation was noted in pancreatic cancer cells [167], where after suppressing STAT3 expression using STAT3 short hairpin RNA (shRNA) expression vectors, the malignancy and metastasis of pancreatic cancer.
cells remarkably reduced. Besides, the mRNA expression of matrix metalloproteinase-2 (MMP-2) and the vascular endothelial growth factor (VEGF) underwent down-regulation after STAT3 knockdown, demonstrating the pivotal role of STAT proteins in progression of cancer cells. In spite of much progress in cancer therapy and developing novel drugs targeting various signaling pathways, scientists are not yet able to effectively remedy this life threatening condition. Another study puts emphasis on the potential role of STAT3, STAT5A and STAT5B in the malignancy and invasion of leukemia. In this study, K-562 cells were transfected by anti-STAT3, anti-STAT5A and anti-STAT5B small interfering RNAs (siRNAs). Importantly, the expression of mentioned STAT proteins significantly reduced. It was found that preventing the expression of STAT3, STAT5A and STAT5B is related to the enhanced apoptosis in cancer cells [168]. Finding a new way in treatment of astrocytoma attracts much attention due to the high incident rate of this primary central nervous system tumor. Based on the vital role of STAT3 in the malignancy of tumor cells, inhibition of STAT3 in astrocytoma cells can diminish the mortality resulted from this disorder [169]. STAT3 knockdown promotes the sensitivity of astrocytoma cells into apoptosis.

Furthermore, in respect to the role of STAT3 in inducing the expression of anti-apoptotic factors such as Bcl-xL and survivin, down-regulation of STAT3 is related to the decreased viability and proliferation of cancer cells. However, scientists have faced challenges in the treatment of other brain tumors, particularly glioblastoma. In spite of much effort in the treatment of glioblastoma, it still remains one of the most malignant brain tumors [170]. The capabilities of cells to initiate, progress and recur have led to the high malignancy of these tumor cells [171–175]. Gene manipulation is of importance in reducing the malignancy of glioblastoma cells. Interestingly, inhibition of STAT3 using RNAi can stimulate apoptotic cell death in glioblastoma cells by upregulation of caspase-3 and BAX, and down-regulation of Bcl-2 and cyclin-D. Besides, STAT3 inhibition decreases the CD133+ cell proportion and subsequently, sensitizes cancer cells to apoptosis [176]. On the other hand, one of the difficulties in radio- and chemo-therapy is the resistance of cancer cells. Investigation of molecular signaling pathways and subsequently, regulation of them can be beneficial in enhancing the efficacy of radio- and chemo-therapy. It seems that STAT3 knockdown remarkably elevates the efficacy of radio-therapy in laryngeal carcinoma by reducing the expression of Bcl-2 and VEGF, and enhancing the number of apoptotic cell death [177]. These studies obviously highlight this fact that STAT proteins have vital roles in migration, proliferation and malignancy of cancer cells and modulation of their expression using RNAi interference is a great strategy in combating cancer cells.

6. Nano-Technological Approaches for Targeting STATs

6.1. Nanoparticles

6.1.1. In Vitro

Based on the statistics reported by American Cancer Society, the efforts for management of cancer should be continued to prevent the high mortality and morbidity associated with this life threatening condition [178]. Cancer cells apply various signaling pathways to ensure their progression. These dynamic and flexible molecular pathways provide a challenge in the treatment of cancer [9,179,180]. On the other hand, although anti-tumor drugs targeting signaling pathways have been introduced in cancer therapy, low bioavailability and lack of targetability diminish the anti-tumor activity of these drugs. To date, NPs have been used for the treatment of various pathological disorders [180] and this capability has been applied in cancer therapy. Hydroxyapatite (HAP) is an important biomaterial with extensive applications in tissue engineering and bone repair [181,182]. HAP has demonstrated great potential in the delivery of DNA and proteins due to its excellent properties such as biocompatibility and porosity [183]. HAP-based NPs can be considered as a promising strategy in the delivery of anti-STAT3 shRNA. HAP NPs effectively deliver anti-STAT3 shRNA to prostate cancer cells leading to the induction of apoptosis and decreased viability of cancer cells. During this transfection, STAT3 down-regulation significantly diminished the expression of Bcl-2, VEGF and cyclin
Furthermore, the expression of caspase-3 and BAX underwent upregulation [184]. SLNs are another option in the delivery of small molecule drugs and genetic materials. High biocompatibility and great stability have resulted in application of SLNs for gene delivery [185]. Loading a STAT3 inhibitor on SLNs is of importance in combating lung cancer cells. SLNs protected genetic materials against DNasel and serum-mediated degradation. Encapsulation of DNA by SLNs preserved its supercoiled and circular formation. STAT3 inhibitor-loaded SLNs significantly sensitized lung cancer cells to cisplatin-mediated apoptosis (Table 3) [186]. In respect to the potential role of STAT3 in enhancing the malignancy of cancer cells [187], this signaling pathway has obtained much attention in triple negative breast cancer (TNBC) therapy and a number of drugs approved by the Food and Drug Administration (FDA) such as niclosamide have been used in treatment of TNBC as inhibitors of STAT3 [188]. In accordance to the efficacy of SLNs in the delivery of STAT inhibitors, loading a STAT3 inhibitor on SLNs remarkably decreases the viability of cancer cells by stimulation of apoptosis via down-regulation of STAT3 phosphorylation [13]. SLNs have been applied in treatment of ovarian cancer due to their potential in delivery of STAT3 siRNA and consequently, stimulation of apoptotic cell death through down-regulation of Bcl-2 and survivin [189].

Accumulating data demonstrates that SHP-1 may be able to modulate stemness and the epithelial-to-mesenchymal transition (EMT) of tumor cells by targeting the JAK2/STAT3 signaling pathway [190–192]. Therefore, NP-mediated SHP-1 regulation is of interest in cancer therapy. ZnAs@SiO$_2$ NPs use the same strategy in reducing hepatocellular carcinoma malignancy. It seems that application of ZnAs@SiO$_2$ NPs significantly diminishes the expression of stemness markers such as CD133, Sox-2 and Oct-4. Besides, these NPs are capable of induction of apoptotic cell death and reducing the metastasis and migration of hepatocellular carcinoma cells by EMT inhibition. These anti-tumor activities arise as a result of disruption in the SHP-1/JAK2/STAT3 signaling pathway [193]. Receptor-targeted delivery enhances the capability of NPs in decreasing the viability of cancer cells. It has been demonstrated that CD38 has a minimal expression in normal cells, while its overexpression occurs in multiple myeloma (MM) cells [194]. There have been efforts to target CD38 at MM cells and daratumumab has been used for this purpose [195–197]. Moreover, anti-CD38-decorated NPs carrying the STAT3 inhibitor have been reported to have high cellular uptake with great anti-tumor activity [198].

Poly(lactic-co-glycolic acid) (PLGA) has a variety of excellent properties such as biocompatibility and biodegradability. FDA has approved the application of PLGA for human uses. PLGA NPs have a size similar to pathogens leading to their phagocytosis by dendritic cells (DCs). This feature has resulted in application of PLGA NPs for delivery of drugs into DCs [199–204]. It appears that PLGA provides a suitable platform for conjugation of JSI-124, as a STAT3 inhibitor. JSI-124 PLGA NPs have great anti-tumor activity against B16 melanoma cells by reducing the expression of STAT3 in DCs and enhancing the function of DCs in terms of promoting the production of T cells leading to the cancer immunotherapy [205]. The capability of PLGA NPs in releasing drugs in a sustained-released behavior is of importance in co-delivery of paclitaxel, a chemotherapeutic agent and STAT siRNA to sensitize lung cancer cells to apoptotic cell death [206]. Taking everything into account, in respect to the ability of PLGA NPs in delivery, anti-STAT3-loaded PLGA NPs can be considered as promising agents in cancer immunotherapy by targeting DCs [207]. It has been demonstrated that STAT3-siRNA-loaded NPs have high cellular uptake by tumor cells leading to their high efficacy in reducing the malignancy of cancer cells. It appears that clathrin-mediated endocytosis participates in cellular uptake of STAT3-siRNA-loaded NPs by melanoma cells [208].

6.1.2. In Vivo

Melanoma is one of the malignant skin cancers that proliferation of pigment producing melanocytes occurs in the epidermis. Surgery and chemotherapy are considered as current strategies in melanoma therapy [209–211]. However, one of the problems associated with chemotherapy is the resistance of tumor cells [29]. Using gene therapy enhances the anti-tumor activity of chemotherapeutic agents.
Co-delivery of imatinib and anti-STAT3 siRNA (non-invasive topical iontophoretic administration) using gold NPs is related to a remarkable decrease in tumor volume and tumor weight in melanoma tumor bearing mice, showing the efficacy of gold NPs in treatment of melanoma by inhibition of STAT3 [212]. Erlotinib (ELTN) is extensively used in chemotherapy with the capability of targeting epidermal growth factor receptor (EGFR) gene. However, resistance of cancer cells challenges the potential of this agent in chemotherapy [213,214]. Fedratinib (FDTN) is a small molecule known as the JAK2 inhibitor and is applied in the treatment of myelofibrosis [215]. Co-administration of ELTN and FDTN using biodegradable NPs leads to the satisfactory results in ELTN-resistance non-small cell-lung cancer (NSCLC) cells. The biodegradable NPs had great stability and effectively released drug at mild acidic pH of the tumor microenvironment. Loading a combination of ELTN and FDTN on NPs not only enhances the anti-tumor activity by inhibition of the JAK2/STAT3 signaling pathway, but also diminishes the systemic adverse effects [216]. As it was mentioned, HAP has human applications due to its high biocompatibility. Besides, it seems that HAP has anti-tumor activity making its appropriate for cancer therapy [217–223]. HAP NPs are capable of inhibiting the progression and invasion of prostate tumor cells in mouse model by reducing the expression of STAT3 resulting in down-regulation of Bcl-2, VEGF and cyclin D1 [224]. A newly developed nanocarrier for the delivery of siRNA should be capable of protection of siRNA against degradation, promoting siRNA potency and simultaneously, improving the biodistribution and pharmacokinetics [224]. Polymeric NPs have demonstrated great potential in this field and polyethyleneimine is among them [225–228]. Loading STAT3 siRNA on lipid-substituted PEI is associated with decreased viability and proliferation of tumor cells by upregulation of caspase-3 and IL-6, and down-regulation of STAT3 and VEGF [229].

5′,2′,4′-trihydroxy-6,7,5′-trimethoxyflavone (TTF1) is a naturally occurring compound exclusively found in Sorbaria sorbifolia (SS) [230,231]. TTF1 has great pharmacological effects such as anti-tumor activity. However, low bioavailability and biodegradation restrict the therapeutic activities of TTF1 [232]. TTF1-loaded NPs are able to remarkably suppress angiogenesis and metastasis of human hepatoma cancer cells by down-regulation of STAT3. It appears that decreased invasion of cancer cells is a consequence of MMP-2 and MMP-9 down-regulation. Besides, anti-angiogenic effect of TTF1-NPs is mediated by reducing the expression of VEGF [233]. BBB is considered as one of the most challenging problems in penetration of drugs into brain. PEI-PLGA NPs solve this problem by enhancing the crossing of STAT3 siRNA through BBB [234].

6.2. Liposomes

6.2.1. In Vivo

It seems that liposomes are potential candidates in the treatment of skin cancer. This notion emanates from the capability in crossing over the stratum corneum layer of skin [235]. It has been demonstrated that edge activators (transferosomes)- or ethanol (ethosomes)-based liposomes are able to deeply penetrate into the skin [236]. Besides, physical techniques such as iontophoresis have enhanced the penetration potential of liposomes into the skin [237–240]. Therefore, liposomes can serve as promising candidates for delivery of STAT proteins in the treatment of skin cancers [241]. It appears that curcumin- and STAT3 siRNA-loaded liposomes significantly down-regulate the expression of STAT3 protein leading to the inhibition of tumor invasion and a remarkable reduction in tumor weight and tumor volume [242].

6.2.2. In Vitro

Targeting tumor-associated macrophages (TAMs) is of importance in cancer therapy due to the potential role of TAMs in the tumor microenvironment and enhancing the malignancy, invasion, angiogenesis and resistance of cancer cells [243,244]. It is held that enhanced TAM-infiltration is associated with a decrease in survival time of patients with cancer [245–247]. Notably, disruption in the STAT3 signaling pathway effectively promotes anti-tumor immunity by enhancing the production
of TNF-α and stimulation of M1-like reprogramming of macrophages [248–252]. Hence, providing STAT3 modulation in macrophages is of interest in improving anti-tumor immunity. CD163-targeted crosolic acid-containing liposomes prevent the expression of STAT3 in macrophages, resulting in enhanced anti-tumor immunity by increasing TNF-α, IFN-γ, IL-12 and IL-2 levels, and decreasing the IL-10 level [245]. Similar to in vivo findings, co-delivery of curcumin and STAT3 by deformable cationic liposomes is associated with cell growth inhibition and apoptosis induction. It is held that clathrin-induced endocytosis mediates the penetration of liposomes into skin [241].

6.3. Micelles

In Vitro and In Vivo

Micelles were first introduced in 1984 for the delivery of drugs [253,254]. Micelles are able to remarkably improve the bioavailability and anti-tumor activity of drugs [255,256]. It seems that polymeric micelles have higher permeability and retention effect compared to the conventional micellar nanocarriers [257,258] making them appropriate for drug delivery. There are two studies that have investigated the efficiency of micellar NPs in the delivery of STAT inhibitors in melanoma cells both in vitro and in vivo. It was found that administration of STAT3 inhibitor-loaded polymeric micelles results in apoptotic cell death in melanoma cells and down-regulates VEGF expression. Besides, these nanocarriers have greater biocompatibility and improve anti-tumor immunity by enhancing DC-mediated IL-12 production [259,260]. The potential application of nanoparticles in targeting STATs is summarized in Figure 1.

Figure 1. Application of nanoparticles in targeting STATs.
Table 3. Potential use of nanocarriers for delivery of STAT inhibitors.

| Nano-carriers                        | Agent                          | In vitro/In vivo | Cell Line/Animal Model | Major Outcomes                                                                 | Refs   |
|--------------------------------------|--------------------------------|------------------|------------------------|--------------------------------------------------------------------------------|--------|
| Gold nanoparticle                    | STAT3 siRNA and imatinib       | In vitro and in vivo | B16F10 (melanoma cells) and tumor bearing C57BL/6 mice | In vitro: Inhibition of tumor growth and decreased expression of STAT3. In vivo: Decreased weight and volume of tumor, reduced expression of STAT3. | [212]  |
| Hydroxyapatite nanoparticles         | Plasmid-based STAT3 siRNA      | In vivo          | Mouse prostate cancer cells | The downregulation of STAT3 downstream genes such as Bcl-2, VEGF and cyclin D1, and consequently, increased level of apoptosis in cancer cells. | [231]  |
| PLGA nanoparticles                   | siRNA polyplexes               | In vitro         | DCs                    | Downregulation of STAT3 expression and increased level of maturation and functionality in DCs. | [207]  |
| Micelle                              | STAT3 siRNA                    | In vivo          | Mice with tumor-associated DCs (TADCs) | Downregulation of STAT3 and stimulation of maturation and activation in TADCs. | [261]  |
| Solid lipid nanoparticle             | STAT3 decoy oligodeoxynucleotides | In vitro          | Human ovarian cancer cell lines A2780 and SKOV3 | Inhibition of STAT3 pathway, stimulation of cell death via increased expression of Bax, Beclin-1, caspase-3 and LC3-II, and prevention of invasion via upregulation of E-cadherin and downregulation of Snail and MMP-9. | [189]  |
| PEI-PLGA-FITC nanoparticles          | siRNA targeting STAT3          | In vitro and in vivo | A549 cells and Balb/c mice | In vitro: Reduced rate of viability in A549 cells. In vivo: Upregulation of caspase-3 and downregulation of IL-6 in mice. | [234]  |
| Liposome                             | shRNA against STAT3            | In vitro         | Ovarian cancer cell lines A2780CP and A2780ss | Increased level of apoptosis and inhibition of cell proliferation. | [262]  |
| Poly (D,L-lactic-co-glycolic-acid) nanoparticle | JSI-124 (STAT3 inhibitor)     | In vitro         | DCs                    | Improved function of DCs and increased level of T cell proliferation. | [205]  |
| Ultrasound-targeted microbubble destruction | Transcription factor decoy of STAT3 | In vivo          | Squamous cell tumors | Downregulation of STAT3 and inhibition of tumor growth. | [263]  |
| Deformable cationic liposomes        | Curcumin and STAT3 siRNA       | In vitro         | Human epidermoid (A431) cancer cells | Inhibition of cancer cell growth and stimulation of apoptosis. | [241]  |
| Lipid-substituted polyethylenimine   | STAT3 siRNA                    | In vitro         | Murine B16.F10 melanoma cells | Remarkable inhibition of STAT3 expression and induction of apoptosis. | [229]  |
Table 3. Cont.

| Nano-carriers                                                                 | Agent                           | In vitro/In vivo | Cell Line/Animal Model                        | Major Outcomes                                                                                                                                           | Refs      |
|--------------------------------------------------------------------------------|---------------------------------|------------------|------------------------------------------------|-----------------------------------------------------------------------------------------------------------------------------------------------------------|-----------|
| Inorganic kernel-supported asymmetric hybrid vesicles                         | STAT3-decoy oligonucleotide    | In vivo          | Nude mice bearing BT474R breast cancer xenograft | Significant inhibition of tumor growth and prevention of trastuzumab resistance                                                                          | [264]     |
| Self-Associating Poly(ethylene oxide)-block-poly(α-carboxyl-ε-caprolactone) Drug Conjugates | JSI-124 (STAT3 inhibitor)      | In vitro         | B16F10 melanoma cells and tumor exposed bone marrow derived dendritic cells | Inhibition of STAT3 and great anti-tumor activity                                                                                                     | [265]     |
| E-selectin thioaptamer-conjugated multistage vector                           | siRNA                           | In vivo          | Mice bearing metastatic breast cancer and murine xenograft models of human MDA-MB-231 breast tumor | Downregulation of STAT3 as much as 48.7% in cancer cells inside bone marrow, and increased rate of survival in mice                                      | [266]     |
| Lipid-substituted polyethyleneimine                                          | siRNA polyplexes               | In vitro         | Wild-type MDA-MB-435 breast cancer cells        | Downregulation of STAT3 and decreased viability of cells                                                                                            | [267]     |
| Polymeric nanoparticles                                                       | STAT6                           | In vitro and in vivo | HeLa cells and tumor bearing mice               | In vitro: knockdown of IFN-γR2 and stimulation of cell death in HeLa human epithelial cells                                                   | [268]     |
|                                                                                 |                                 |                  |                                                | In vivo: decreased volume of tumor and increased rate of survival                                                                             |           |
| Gold nanoparticles                                                            | STAT3 siRNA                    | In vitro         | B16F10 murine melanoma cells                   | Remarkable inhibition of cancer cell growth                                                                                                          | [208]     |
| Lipid nanoparticle                                                            | RNAi-mediating plasmid DNA      | In vitro         | Chemoresistant Calu1 cells                     | Downregulation of STAT3 and resensitize Calu human lung cancer cells to chemotherapy (cisplatin)                                                  | [186]     |
| PLGA nanoparticles                                                             | JSI-124 (STAT3 inhibitor)      | In vivo          | C57BL/b male mice                              | Great anti-tumor impact                                                                                                                            | [269]     |
| Dissolving microneedles                                                        | STAT3 siRNA                    | In vivo          | Female C57BL/b mice                            | Great gene silencing and inhibition of tumor cell growth                                                                                  | [270]     |
7. Conclusion and Future Trends

In respect to the vital role of STAT proteins in various important biological processes including cell cycle, differentiation, apoptosis and cell proliferation, any impairment in the STAT signaling pathway is associated with the development of pathological conditions, particularly cancer. As a consequence, targeting the STAT signaling pathway has demonstrated a great potential in cancer therapy. On the other hand, there have been some difficulties in the delivery of drugs that target the STAT signaling pathway. Therefore, it seems that application of nanocarriers for loading STAT modulators may be important in terms of releasing drug into the tumor site and inhibition of resistance of cancer cells by loading the optimum amount of drug. Until now, various nanoparticles have been designed for targeting the STAT signaling pathway, especially STAT3, which include gold nanoparticles, hydroapatite nanocarriers, PLGA nanoparticles, micelles, solid lipid nanoparticles, liposomes and microbubbles. These nanocarriers have been applied in various cancers both in vitro and in vivo, and exhibited high potentiality in reducing the viability, migration and malignancy of tumor cells by regulating the expression of STAT proteins. However, more studies are needed to elucidate the efficacy of nanoparticles in targeting the STAT signaling pathway for cancer therapy. Although huge emphasis has been put on the capabilities and benefits of using NPs in delivery of STAT to cancer cells, it has been reported that only 0.7% of administered NPs are found to be delivered to the tumor site, thereby challenging the potential role of NPs in drug delivery [271]. This issue needs to be carefully addressed in future studies.

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**Abbreviations**

| Abbreviation | Definition                          |
|--------------|------------------------------------|
| BBB          | blood-brain barrier                |
| NPs          | nanoparticles                       |
| STAT         | signal transducers and activator of transcription |
| DRE          | DNA regulatory elements             |
| Tyr          | tyrosine                           |
| GAS          | gamma-activated sites              |
| ISREs        | interferon-stimulated response elements |
| IFN          | interferon                         |
| SCOS         | suppressor of cytokine signaling   |
| PTP          | protein tyrosine phosphatase       |
| PIAS         | protein inhibitors of activated STATs |
| IL           | interleukin                        |
| CRC          | colorectal cancer                  |
| IncRNA       | long non-coding RNA                |
| miR          | microRNA                           |
| Cys          | cysteine                           |
| AHR          | airway hyper responsiveness        |
| RNAi         | RNA interference                   |
| MMP          | matrix metalloproteinase           |
| VEGF         | vascular endothelial growth factor |
| SLNs         | solid lipid NPs                    |
| HAP          | hydroxyapatite                     |
| TNBC         | triple negative breast cancer      |
| Niclo        | niclosamide                        |
| FDA          | Food and Drug Administration       |
| EMT          | epithelial-to-mesenchymal transition |
| MM           | multiple myeloma                   |
| DCs          | dendritic cells                    |
ELTN  
ERLOTINIB

EGFR  
evader growth factor receptor

FDTN  
evadratinib

NSCLC  
normally cell-lung cancer

PEI  
ployethylenimine

TTF1  
trimethoxyflavone

SS  
Sorbaria sorbitolia

TAM  
tumor-associated macrophage

TADCs  
tumor-associated CDs

JAK  
Janus kinase

References

1. Gao, A.; Hu, X.-L.; Saeed, M.; Chen, B.-F.; Li, Y.-P.; Yu, H.-J. Overview of recent advances in liposomal nanoparticle-based cancer immunotherapy. *Acta Pharmacol. Sin.* 2019, 40, 1129–1137. [CrossRef] [PubMed]

2. Liu, J.; Zhang, R.; Xu, Z.P.S. Nanoparticle-Based Nanomedicines to Promote Cancer Immunotherapy: Recent Advances and Future Directions. *Small* 2019, 15, 1900262. [CrossRef] [PubMed]

3. Ferrari, M. Cancer nanotechnology: Opportunities and challenges. *Nat. Rev. Cancer* 2005, 5, 161. [CrossRef] [PubMed]

4. Singh, R.P.; Sharma, G.; Kumari, L.; Koch, B.; Singh, S.; Bharti, S.; Rajinikanth, P.S.; Pandey, B.L.; Muthu, M.S. RGD-TPGS decorated theranostic liposomes for brain targeted delivery. *Colloids Surf. B Biointerfaces* 2016, 147, 129–141.

5. Wan, L.; Pantel, K.; Kang, Y. Tumor metastasis: Moving new biological insights into the clinic. *Nat. Med.* 2013, 19, 1450. [CrossRef] [PubMed]

6. Barker, H.E.; Paget, J.T.; Khan, A.A.; Harrington, K.J. The tumour microenvironment after radiotherapy: Mechanisms of resistance and recurrence. *Nat. Rev. Cancer* 2015, 15, 409. [CrossRef] [PubMed]

7. Ahmadi, Z.; Mohammadinejad, R.; Ashrafizadeh, M. Drug delivery systems for resveratrol, a non-flavonoid polyphenol: Emerging evidence in last decades. *J. Drug Deliv. Sci. Technol.* 2019, 51, 591–604. [CrossRef]

8. Machado, N.D.; Fernández, M.A.; Díaz, D.D. Recent Strategies in Resveratrol Delivery Systems. *ChemPlusChem* 2019, 84, 951–973. [CrossRef]

9. Ashrafizadeh, M.; Mohammadinejad, R.; Tavakol, S.; Ahmadi, Z.; Roomiani, S.; Katebi, M. Autophagy, anoikis, ferroptosis, necroptosis, and endoplasmic reticulum stress: Potential applications in melanoma therapy. *J. Cell. Physiol.* 2019, 234, 19471–19479. [CrossRef]

10. Rawal, S.; Patel, M.M. Threatening cancer with nanoparticle aided combination oncotherapy. *J. Control. Release* 2019, 301, 76–109. [CrossRef] [PubMed]

11. Johnsen, K.B.; Moos, T. Revisiting nanoparticle technology for blood–brain barrier transport: Unfolding at the endothelial gate improves the fate of transferrin receptor-targeted liposomes. *J. Control. Release* 2016, 222, 32–46. [CrossRef] [PubMed]

12. Muhammad, T.; Zhang, F.; Zhang, Y.; Liang, Y. RNA interference: A natural immune system of plants to counteract biotic stressors. *Cells* 2019, 8, 38. [CrossRef] [PubMed]

13. Pindiprolu, S.K.S.; Chintamaneni, P.K.; Krishnamurthy, P.T.; Ratna Sree Ganapathineedi, K. Formulation-optimization of solid lipid nanocarrier system of STAT3 inhibitor to improve its activity in triple negative breast cancer cells. *Drug Dev. Ind. Pharm.* 2019, 45, 304–313. [CrossRef] [PubMed]

14. Askarizadeh, A.; Butler, A.E.; Badiee, A.; Sahebkar, A. Liposomal nanocarriers for statins: A pharmacokinetic and pharmacodynamics appraisal. *J. Cell. Physiol.* 2019, 234, 1219–1229. [CrossRef] [PubMed]

15. Rouholamini, S.E.Y.; Moghassemi, S.; Maharat, Z.; Hakamivala, A.; Kashanian, S.; Omidfar, K. Effect of silibinin-loaded nano-niosomal coated with trimethyl chitosan on miRNAs expression in 2D and 3D models of T47D breast cancer cell line. *Artif. Cells Nanomed. Biotechnol.* 2018, 46, 524–535. [CrossRef] [PubMed]

16. Gao, Y.-E.; Bai, S.; Ma, X.; Zhang, X.; Hou, M.; Shi, X.; Huang, X.; Chen, J.; Wen, F.; Xue, P. Codelivery of Doxorubicin and Camptothecin by Dual-responsive Unimolecular Micelle-based β-cyclodextrin for Enhanced Chemotherapy. *Colloids Surf. B Biointerfaces* 2019, 183, 110428. [CrossRef] [PubMed]
17. Nadimi, A.E.; Ebrahimipour, S.Y.; Afshar, E.G.; Falahati-Pour, S.K.; Ahmadi, Z.; Mohammadinejad, R.; Mohamadi, M. Nano-scale drug delivery systems for antiarrhythmic agents. Eur. J. Med. Chem. 2018, 157, 1153–1163. [CrossRef] [PubMed]

18. Jafari, R.; Zolbanin, N.M.; Majidi, J.; Atyabi, F.; Yousefi, M.; Jadidi-Niaragh, F.; Aghabati-Maleki, L.; Shanihebandi, D.; Zangbar, M.-S.S.; Rafatpanah, H. Anti-Mucin1 Aptamer-Conjugated Chitosan Nanoparticles for Targeted Co-Delivery of Docetaxel and IGF-1R siRNA to SKBR3 Metastatic Breast Cancer Cells. Iran. Biomed. J. 2019, 23, 21–33. [CrossRef]

19. Misra, S.K.; De, A.; Pan, D. Targeted delivery of STAT-3 modulator to breast cancer stem-like cells downregulates a series of stemness genes. Mol. Cancer Ther. 2018, 17, 119–129. [CrossRef]

20. Mohammadinejad, R.; Dadashzadeh, A.; Moghassemi, S.; Ashrafizadeh, M.; Dehshahri, A.; Pardakhty, A.; Sassan, H.A.; Sohevradi, S.M.; Mandegary, A. Shedding light on gene therapy: Carbon dots for the minimally invasive image-guided delivery of plasmids and noncoding RNAs. J. Adv. Res. 2019, 22, 81–93. [CrossRef]

21. Le, D.H.; Commandeur, U.; Steinmetz, N.F. Presentation and Delivery of Tumor Necrosis Factor-Related Apoptosis-Inducing Ligand via Elongated Plant Viral Nanoparticle Enhances Antitumor Efficacy. ACS Nano 2019, 13, 2501–2510. [CrossRef] [PubMed]

22. Sinha, A.; Chakraborty, A.; Jana, N.R. Dextran-gated, multifunctional mesoporous nanoparticle for glucose-responsive and targeted drug delivery. ACS Appl. Mater. Interfaces 2014, 6, 22183–22191. [CrossRef] [PubMed]

23. Peng, C.; Xu, J.; Yu, M.; Ning, X.; Huang, Y.; Du, B.; Hernandez, E.; Kapur, P.; Hsieh, J.T.; Zheng, J. Tuning the In Vivo Transport of Anticancer Drugs Using Renal-Clearable Gold Nanoparticles. Angew. Chem. 2019, 131, 8567–8571.

24. Mu, Q.; Kievit, F.M.; Kant, R.J.; Lin, G.; Jeon, M.; Zhang, M. Anti-HER2/neu peptide-conjugated iron oxide nanoparticles for targeted delivery of paclitaxel to breast cancer cells. Nanoscale 2015, 7, 18010–18014. [CrossRef] [PubMed]

25. Davarani, F.-H.; Ashrafizadeh, M.; Riseh, R.S.; Afshar, E.G.; Mohammad, H.; Razavi, S.H.; Mandegary, A.; Mohammadinejad, R. Antifungal nanoparticles reduce aflatoxin contamination in pistachio. PHJ 2018, 1, 26–33.

26. Saulite, L.; Pleiko, K.; Popena, I.; Dapkute, D.; Rotomskis, R.; Riekstina, U. Nanoparticle delivery to metastatic breast cancer cells by nanoengineered mesenchymal stem cells. Beilstein J. Nanotechnol. 2018, 9, 321–332. [CrossRef] [PubMed]

27. Feng, T.; Ai, X.; Ong, H.; Zhao, Y. Dual-responsive carbon dots for tumor extracellular microenvironment triggered targeting and enhanced anticancer drug delivery. ACS Appl. Mater. Interfaces 2016, 8, 18732–18740. [CrossRef] [PubMed]

28. Truffi, M.; Colombo, M.; Sorrentino, L.; Pandolfi, L.; Mazzucchelli, S.; Pappalardo, F.; Pacini, C.; Allevi, R.; Bonizzi, A.; Corsi, F. Multivalent exposure of trastuzumab on iron oxide nanoparticles improves antitumor potential and reduces resistance in HER2-positive breast cancer cells. Sci. Rep. 2018, 8, 6563. [CrossRef] [PubMed]

29. Ahmadi, Z.; Roomiani, S.; Bemani, N.; Ashrafizadeh, M. The Targeting of Autophagy and Endoplasmic Reticulum Stress Mechanisms by Honokiol Therapy. Rev. Clin. Med. 2019, 6, 66–73.

30. Daulat, A.M.; Wagner, M.S.; Walton, A.; Baudelet, E.; Audebert, S.; Camoin, L.; Borg, J.P. The Tumor Suppressor SCRIB is a Negative Modulator of the Wnt/beta-Catenin Signaling Pathway. Proteomics 2019, e1800487. [CrossRef]

31. Liu, S.; Wang, Q.; Liu, Y.; Xia, Z.Y. miR-425-5p suppresses tumorigenesis and DDP resistance in human-prostate cancer by targeting GSK3beta and inactivating the Wnt/beta-catenin signaling pathway. J. Biosci. 2019, 44, 102. [CrossRef] [PubMed]

32. Xie, W.; Zhang, Y.; Zhang, S.; Wang, F.; Zhang, K.; Huang, Y.; Zhou, Z.; Huang, G.; Wang, J. Oxymatrine enhanced anti-tumor effects of Bevacizumab against triple-negative breast cancer via abating Wnt/beta-Catenin signaling pathway. Am. J. Cancer Res. 2019, 9, 1796–1814. [PubMed]

33. Ahmadi, Z.; Ashrafizadeh, M. Melatonin as a potential modulator of Nrf2. Fundam. Clin. Pharmacol. 2019. [CrossRef] [PubMed]

34. Woo, C.C.; Hsu, A.; Kumar, A.P.; Sethi, G.; Tan, K.H.B. Thymoquinone inhibits tumor growth and induces apoptosis in a breast cancer xenograft mouse model: The role of p38 MAPK and ROS. PloS ONE 2013, 8, e75356. [CrossRef] [PubMed]
35. Nair, A.S.; Shishodia, S.; Ahn, K.S.; Kunnumakkara, A.B.; Sethi, G.; Aggarwal, B.B. Deguelin, an Akt inhibitor, suppresses IkBα kinase activation leading to suppression of NF-κB-regulated gene expression, potentiation of apoptosis, and inhibition of cellular invasion. *J. Immunol.* 2006, 177, 5612–5622. [CrossRef] [PubMed]

36. Chua, A.W.L.; Hay, H.S.; Rajendran, P.; Shannumag, M.K.; Li, F.; Bist, P.; Kosay, E.S.; Lim, L.H.; Kumar, A.P.; Sethi, G. Butein downregulates chemokine receptor CXCR4 expression and function through suppression of NF-κB activation in breast and pancreatic tumor cells. *Biochem. Pharmacol.* 2010, 80, 1553–1562. [CrossRef]

37. Singh, S.S.; Yap, W.N.; Arfuso, F.; Kar, S.; Wang, C.; Cai, W.; Dharmarajan, A.M.; Sethi, G.; Kumar, A.P. Targeting the PI3K/Akt signaling pathway in gastric carcinoma: A reality for personalized medicine? *World J. Gastroenterol.* 2015, 21, 12261. [CrossRef]

38. Darnell, J.E. STATs and gene regulation. *Science* 1997, 277, 1630–1635. [CrossRef]

39. Cui, C.; Cheng, X.; Yan, L.; Ding, H.; Guan, X.; Zhang, W.; Tian, X.; Hao, C. Downregulation of TfR1 promotes progression of colorectal cancer via the JAK/STAT pathway. *Cancer Manag. Res.* 2019, 11, 6323. [CrossRef]

40. de Haas, N.; de Koning, C.; di Blasio, S.; Fl...
56. Moshapa, F.T.; Riches-Suman, K.; Palmer, T.M. Therapeutic Targeting of the Proinflammatory IL-6-JAK/STAT Signalling Pathways Responsible for Vascular Restenosis in Type 2 Diabetes Mellitus. *Cardiol. Res. Pract.* 2019, 2019, 9846312. [CrossRef]

57. Mogensen, T.H. IRF and STAT Transcription Factors—From Basic Biology to Roles in Infection, Protective Immunity, and Primary Immunodeficiencies. *Front. Immunol.* 2019, 9, 3047. [CrossRef] [PubMed]

58. Trivedi, S.; Starz-Gaiano, M. Drosophila Jak/STAT Signaling: Regulation and Relevance in Human Cancer and Metastasis. *Int. J. Mol. Sci.* 2018, 19, 4056. [CrossRef]

59. Ko, Y.S.; Rugira, T.; Jin, H.; Park, S.W.; Kim, H.J. Oleandrin and Its Derivative Odoroside A, Both Cardiac Glycosides, Exhibit Anticancer Effects by Inhibiting Invasion via Suppressing the STAT-3 Signaling Pathway. *Int. J. Mol. Sci.* 2018, 19, 3350. [CrossRef] [PubMed]

60. Stabile, H.; Scarno, G.; Fionda, C.; Gismondi, A.; Santoni, A.; Gadina, M.; Sciume, G. JAK/STAT signaling in regulation of innate lymphoid cells: The gods before the guardians. *Immunol. Rev.* 2018, 286, 148–159. [CrossRef]

61. Chen, X.; Vinkemeier, U.; Zhao, Y.; Jeruzalmi, D.; Darnell, J.E., Jr.; Kuriyan, J. Crystal structure of a tyrosine phosphorylated STAT-1 dimer bound to DNA. *Cell* 1998, 93, 827–839. [CrossRef]

62. Pranada, A.L.; Metz, S.; Herrmann, A.; Heinrich, P.C.; Muller-Newen, G. Real time analysis of STAT3 nucleocytoplasmic shuttling. *J. Biol. Chem.* 2004, 279, 15114–15123. [CrossRef] [PubMed]

63. Rawlings, J.S.; Rosler, K.M.; Harrison, D.A. The JAK/STAT signaling pathway. *J. Cell Sci.* 2004, 117, 1281–1283. [CrossRef] [PubMed]

64. Zhang, J.-G.; Metcalf, D.; Rakar, S.; Asimakis, M.; Greenhalgh, C.J.; Willson, T.A.; Starr, R.; Nicholson, S.E.; Carter, W.; Alexander, W.S. The SOCS box of suppressor of cytokine signaling-1 is important for inhibition of cytokine action in vivo. *Proc. Natl. Acad. Sci. USA* 2001, 98, 13261–13265. [CrossRef] [PubMed]

65. Cohney, S.J.; Sanden, D.; Cacalano, N.A.; Yoshimura, A.; Mui, A.; Migone, T.S.; Johnston, J.A. SOCS-3 is tyrosine phosphorylated in response to interleukin-2 and suppresses STAT5 phosphorylation and lymphocyte proliferation. *Mol. Cell. Biol.* 1999, 19, 4980–4988. [CrossRef] [PubMed]

66. Krebs, D.L.; Hilton, D.J. SOCS proteins: Negative regulators of cytokine signaling. *Stem Cells* 2001, 19, 378–387. [CrossRef] [PubMed]

67. Buttarelli, M.; Babini, G.; Raspaglio, G.; Filippetti, F.; Battaglia, A.; Ciucci, A.; Ferrandina, G.; Petrillo, M.; Marino, C.; Mancuso, M. A combined ANXA2-NDRG1-STAT1 gene signature predicts response to chemoradiotherapy in cervical cancer. *J. Exp. Clin. Cancer Res.* 2019, 38, 279. [CrossRef] [PubMed]

68. Yu, L.; Ye, F.; Li, Y.-Y.; Zhan, Y.-Z.; Liu, Y.; Yan, H.-M.; Fang, Y.; Xie, Y.-W.; Zhang, F.-J.; Chen, L.-H. Histone methyltransferase SETDB1 promotes colorectal cancer proliferation through the STAT1-CCND1/CDK6 axis. *Carcinogenesis* 2019. [CrossRef]

69. Jiang, L.; Liu, J.-Y.; Shi, Y.; Tang, B.; He, T.; Liu, J.-J.; Fan, J.-Y.; Wu, B.; Xu, X.-H.; Zhao, Y.-L.; et al. MTMR2 promotes invasion and metastasis of gastric cancer via inactivating IFNγ/STAT1 signaling. *J. Exp. Clin. Cancer Res.* 2019, 38, 206. [CrossRef] [PubMed]

70. Gamero, A.M.; Young, M.R.; Mentor-Marcel, R.; Bobe, G.; Scarzello, A.J.; Wise, J.; Colburn, N.H. STAT2 contributes to promotion of colorectal and skin carcinogenesis. *Cancer Prev. Res.* 2010, 3, 495–504. [CrossRef]

71. Hwang, S.T.; Kim, C.; Lee, J.H.; Hwang, S.; Kim, C.; Alharbi, S.A.; Shair, O.H.; Sethi, G.; Ahn, K.S. Cycloastragenol can negate constitutive STAT3 activation and promote paclitaxel-induced apoptosis in human gastric cancer cells. *Phytomedicine* 2019, 59, 152907. [CrossRef] [PubMed]

72. Lee, J.; Kim, C.; Lee, S.-G.; Sethi, G.; Ahn, K. Ophiopogonin d, a steroidal glycoside abrogates STAT3 signaling cascade and exhibits anti-cancer activity by causing GSH/GSSG imbalance in lung carcinoma. *Cancers* 2018, 10, 427. [CrossRef] [PubMed]

73. Lee, J.H.; Kim, C.; Lee, J.; Um, J.-Y.; Sethi, G.; Ahn, K.S. Arctiin is a pharmacological inhibitor of STAT3 phosphorylation at tyrosine 705 residue and potentiates bortezomib-induced apoptotic and angiogenic effects in human multiple myeloma cells. *Phytomedicine* 2019, 55, 282–292. [CrossRef] [PubMed]

74. Loh, C.-Y.; Arya, A.; Naema, A.F.; Wong, W.F.; Sethi, G.; Looi, C.Y. Signal transducer and activator of transcription (stats) proteins in cancer and inflammation: Functions and therapeutic implication. *Front. Oncol.* 2019, 9, 48. [CrossRef]
76. Pan, S.; Deng, Y.; Fu, J.; Zhang, Y.; Zhang, Z.; Ru, X.; Qin, X. TRIM52 promotes colorectal cancer cell proliferation through the STAT3 signaling. *Cancer Cell Int.* 2019, 19, 57. [CrossRef]
77. Yu, Z.Y.; Huang, R.; Xiao, H.; Sun, W.F.; Shan, Y.J.; Wang, B.; Zhao, T.T.; Dong, B.; Zhao, Z.H.; Liu, X.L. Fluacrypyrim, a novel STAT3 activation inhibitor, induces cell cycle arrest and apoptosis in cancer cells harboring constitutively-active STAT3. *Int. J. Cancer* 2010, 127, 1259–1270. [CrossRef] [PubMed]
78. Nishi, M.; Batsaikhan, B.-E.; Yoshikawa, K.; Higashijima, J.; Tokunaga, T.; Takesu, C.; Kashihara, H.; Ishikawa, D.; Shimada, M. High STAT4 Expression Indicates Better Disease-free Survival in Patients with Gastric Cancer. *Anticancer Res.* 2017, 37, 6723–6729.
79. Zhang, Y.; Yu, C. Prognostic values of signal transducers activators of transcription in gastric cancer. *Biosci. Rep.* 2019, 39, BSR20181695. [CrossRef]
80. Zhou, Y.; Zhong, J.-H.; Gong, F.-S.; Xiao, J. MiR-141-3p suppresses gastric cancer induced transition of normal fibroblast and BMSC to cancer-associated fibroblasts via targeting STAT4. *Exp. Mol. Pathol.* 2019, 107, 85–94. [CrossRef]
81. Chen, J.; Gong, C.; Mao, H.; Li, Z.; Fang, Z.; Chen, Q.; Lin, M.; Jiang, X.; Hu, Y.; Wang, W. E2F1/SP3/STAT6 axis is required for IL-4-induced epithelial-mesenchymal transition of colorectal cancer cells. *Int. J. Oncol.* 2018, 53, 567–578. [CrossRef] [PubMed]
82. Miklossy, G.; Hilliard, T.S.; Turkson, J. Therapeutic modulators of STAT signalling for human diseases. *Nat. Rev. Drug Discov.* 2013, 12, 611. [CrossRef] [PubMed]
83. Walker, S.; Xiang, M.; Frank, D. STAT3 Activity and Function in Cancer: Modulation by STAT5 and miR-146b. *Cancers* 2014, 6, 958–968. [CrossRef] [PubMed]
84. Wingelhofer, B.; Neubauer, H.A.; Valent, P.; Han, X.; Constantinescu, S.N.; Gunning, P.T.; Müller, M.; Moriggl, R. Implications of STAT3 and STAT5 signaling on gene regulation and chromatin remodeling in hematopoietic cancer. *Leukemia* 2018, 32, 1713. [CrossRef] [PubMed]
85. Tabassum, S.; Abbasi, R.; Ahmad, N.; Farooqi, A.A. Targeting of JAK-STAT Signaling in Breast Cancer: Therapeutic Strategies to Overcome Drug Resistance. *Adv. Exp. Med. Biol.* 2018, 1152, 271–281. [CrossRef] [PubMed]
86. Drost, J.; Van Jaarsveld, R.H.; Ponsioen, B.; Zimmerlin, C.; Van Boxtel, R.; Buijs, A.; Sachs, N.; Overmeer, R.M.; Offerhaus, G.J.; Begthel, H. Sequential cancer mutations in cultured human intestinal stem cells. *Nature* 2015, 521, 521–526. [CrossRef] [PubMed]
87. Matano, M.; Date, S.; Shimokawa, M.; Takano, A.; Fujii, M.; Ohta, Y.; Watanabe, T.; Kanai, T.; Sato, T. Modeling colorectal cancer using CRISPR–Cas9–mediated engineering of human intestinal organoids. *Nat. Med.* 2015, 21, 256. [CrossRef] [PubMed]
88. Goel, S.; Huang, J.; Klamperf, L. K-Ras intestinal homeostasis and colon cancer. *Curr. Clin. Pharmacol.* 2015, 10, 73–81. [CrossRef] [PubMed]
89. Sakahara, M.; Okamoto, T.; Oyanagi, J.; Takano, H.; Natsume, Y.; Yamanaka, H.; Kusama, D.; Fuejima, M.; Tanaka, N.; Mori, S.; et al. IFN/STAT signaling controls tumorigenesis and the drug response in colorectal cancer. *Cancer Sci.* 2019, 110, 1293. [CrossRef]
90. Dolatabadi, S.; Jonasson, E.; Lindén, M.; Feredyouni, B.; Bäcksten, K.; Nilsson, M.; Martner, A.; Forootan, A.; Fagman, H.; Landberg, G. JAK–STAT signaling controls stem cell properties including chemotherapy resistance in myxoid liposarcoma. *Int. J. Cancer* 2017, 145, 435–449. [CrossRef]
91. Soleimani, A.; Khazaei, M.; Ferns, G.A.; Ryzhikov, M.; Avan, A.; Hassanian, S.M. Role of TGF-β signaling regulatory microRNAs in the pathogenesis of colorectal cancer. *J. Cell. Physiol.* 2019, 234, 14574–14580. [CrossRef] [PubMed]
92. Paseban, M.; Marjaneh, R.M.; Banach, M.; Riahi, M.M.; Bo, S.; Sahebkar, A. Modulation of microRNAs by aspirin in cardiovascular disease. *Trends Cardiovasc. Med.* 2019. [CrossRef] [PubMed]
93. Tajbakhsh, A.; Bianconi, V.; Pirro, M.; Hayat, S.M.G.; Johnston, T.P.; Sahebkar, A. Efferocytosis and Atherosclerosis: Regulation of Phagocyte Function by MicroRNAs. *Trends Endocrinol. Metab.* 2019, 30, 672–683. [CrossRef] [PubMed]
94. Wang, S.; Zhang, S.; He, Y.; Huang, X.; Hui, Y.; Tang, Y. HOXA11-AS regulates JAK-STAT pathway by miR-15a-3p/STAT3 axis to promote the growth and metastasis in liver cancer. *J. Cell. Biochem.* 2019, 120, 15941–15951. [CrossRef] [PubMed]
95. Alston, C.I.; Dix, R.D. SOCSs and Herpesviruses, With Emphasis on Cytomegalovirus Retinitis. *Front. Immunol.* 2019, 10, 732. [CrossRef] [PubMed]
96. Li, M.; Zheng, R.; Yuan, F.L. MiR-410 affects the proliferation and apoptosis of lung cancer A549 cells through regulation of SOCS3/JAK-STAT signaling pathway. *Eur. Rev. Med. Pharmacol. Sci.* 2018, 22, 5987–5993. [CrossRef] [PubMed]

97. Sen, M.; Thomas, S.M.; Kim, S.; Yeh, J.I.; Ferris, R.L.; Johnson, J.T.; Duvvuri, U.; Lee, J.; Sahu, N.; Joyce, S. First-in-human trial of a STAT3 decoy oligonucleotide in head and neck tumors: Implications for cancer therapy. *Cancer Discov.* 2012, 2, 694–705. [CrossRef]

98. Aggarwal, B.B.; Sethi, G.; Baladandayuthapani, V.; Krishnan, S.; Shishodia, S. Targeting cell signaling pathways for drug discovery: An old lock needs a new key. *J. Cell. Biochem.* 2007, 102, 580–592. [CrossRef]

99. Aggarwal, V.; Kashyap, D.; Sak, K.; Tuli, H.S.; Jain, A.; Chaudhary, A.; Garg, V.K.; Sethi, G.; Yerer, M.B. Molecular mechanisms of action of tococtrienols in cancer: Recent trends and advancements. *Int. J. Mol. Sci.* 2019, 20, 656. [CrossRef]

100. Bishayee, A.; Sethi, G. Bioactive natural products in cancer prevention and therapy: Progress and promise. In *Seminars in Cancer Biology*; Academic Press: Cambridge, MA, USA, 2016; pp. 1–3.

101. Chai, E.Z.P.; Shanmugam, M.K.; Arfuso, F.; Dharmarajan, A.; Wang, C.; Kumar, A.P.; Samy, R.P.; Lim, L.H.; Wang, L.; Goh, B.C. Targeting transcription factor STAT3 for cancer prevention and therapy. *Pharmacol. Ther.* 2016, 162, 86–97. [CrossRef]

102. Jung, Y.Y.; Lee, J.H.; Nam, D.; Narula, A.S.; Namjoshi, O.A.; Blough, B.E.; Um, J.-Y.; Sethi, G.; Ahn, K.S. Anti-myelemia effects of icarin are mediated through the attenuation of jak/stat3-dependent signaling cascade. *Front. Pharmacol.* 2018, 9, 531. [CrossRef] [PubMed]

103. Kim, C.; Lee, S.-G.; Yang, W.M.; Arfuso, F.; Um, J.-Y.; Kumar, A.P.; Bian, J.; Sethi, G.; Ahn, K.S. Formononetin-induced oxidative stress abrogates the activation of STAT3/5 signaling axis and suppresses the tumor growth in multiple myeloma preclinical model. *Cancer Lett.* 2018, 431, 123–141. [CrossRef] [PubMed]

104. Baek, S.; Lee, J.; Kim, C.; Ko, J.-H.; Ryu, S.-H.; Lee, S.-G.; Yang, W.; Um, J.-Y.; Chinnathambi, A.; Alharbi, S. Ginkgolic acid C 17: 1, derived from Ginkgo biloba leaves, suppresses constitutive and inducible STAT3 activation through induction of PTEN and SHP-1 tyrosine phosphatase. *Molecules* 2017, 22, 276. [CrossRef] [PubMed]

105. Zhang, J.; Ahn, K.S.; Kim, C.; Shanmugam, M.K.; Siveen, K.S.; Arfuso, F.; Samym, R.P.; Deivasigamanim, A.; Lim, L.H.K.; Wang, L. Nimbolide-induced oxidative stress abrogates STAT3 signaling cascade and inhibits tumor growth in transgenic adenocarcinoma of mouse prostate model. *Antioxid. Redox Signal.* 2016, 24, 575–589. [CrossRef] [PubMed]

106. Baek, S.H.; Ko, J.-H.; Lee, H.; Jung, J.; Kong, M.; Lee, J.-W.; Lee, J.; Chinnathambi, A.; Zayed, M.; Alharbi, S.A. Resveratrol inhibits STAT3 signaling pathway through the induction of SOCS-1: Role in apoptosis induction and radiosensitization in head and neck tumor cells. *Phytomedicine* 2016, 23, 566–577. [CrossRef] [PubMed]

107. Deorukhkar, A.; Krishnan, S.; Sethi, G.; Aggarwal, B.B. Back to basics: How natural products can provide the basis for new therapeutics. *Expert Opin. Investig. Drugs* 2007, 16, 1753–1773. [CrossRef] [PubMed]

108. Sethi, G.; Shanmugam, M.; Warrier, S.; Merarchi, M.; Arfuso, F.; Kumar, A.; Bishayee, A. Pro-apoptotic and anti-cancer properties of diosgenin: A comprehensive and critical review. *Nutrients* 2018, 10, 645. [CrossRef] [PubMed]

109. Shanmugam, M.K.; Kannaiyan, R.; Sethi, G. Targeting cell signaling and apoptotic pathways by dietary agents: Role in the prevention and treatment of cancer. *Nutr. Cancer* 2011, 63, 161–173. [CrossRef] [PubMed]

110. Shanmugam, M.K.; Lee, J.H.; Chai, E.Z.P.; Kanchi, M.M.; Kar, S.; Arfuso, F.; Dharmarajan, A.; Kumar, A.P.; Ramar, P.S.; Looi, C.Y. Cancer prevention and therapy through the modulation of transcription factors by bioactive natural compounds. In *Seminars in Cancer Biology*; Academic Press: Cambridge, MA, USA; pp. 35–47.

111. Shanmugam, M.K.; Nguyen, A.H.; Kumar, A.P.; Tan, B.K.; Sethi, G. Targeted inhibition of tumor proliferation, survival, and metastasis by pentacyclic triterpenoids: Potential role in prevention and therapy of cancer. *Cancer Lett.* 2012, 320, 158–170. [CrossRef]

112. Shrimali, D.; Shanmugam, M.K.; Kumar, A.P.; Zhang, J.; Tan, B.K.; Ahn, K.S.; Sethi, G. Targeted abrogation of diverse signal transduction cascades by emodin for the treatment of inflammatory disorders and cancer. *Cancer Lett.* 2013, 341, 139–149. [CrossRef] [PubMed]
113. Zhang, J.; Sikka, S.; Siveen, K.S.; Lee, J.H.; Um, J.-Y.; Kumar, A.P.; Chinnathambi, A.; Alharbi, S.A.; Rangappa, K.S.; Sethi, G. Cardamomin represses proliferation, invasion, and causes apoptosis through the modulation of signal transducer and activator of transcription 3 pathway in prostate cancer. *Apoptosis* **2017**, *22*, 158–168. [CrossRef] [PubMed]

114. Liu, J.; Qu, L.; Meng, L.; Shou, C. Topoisomerase inhibitors promote cancer cell motility via ROS-mediated activation of JAK2-STAT1-CXCL1 pathway. *J. Exp. Clin. Cancer Res. CR* **2019**, *38*, 370. [CrossRef] [PubMed]

115. Park, S.Y.; Lee, C.J.; Choi, J.H.; Kim, J.H.; Kim, J.W.; Kim, J.Y.; Nam, J.S. The JAK2/STAT3/CCND2 Axis promotes colorectal Cancer stem cell persistence and radioresistance. *J. Exp. Clin. Cancer Res. CR* **2019**, *38*, 399. [CrossRef] [PubMed]

116. Wong, A.L.; Hirpara, J.L.; Pervaiz, S.; Eu, J.-Q.; Sethi, G.; Goh, B.-C. Do STAT3 inhibitors have potential in the future for cancer therapy? *Expert Opin. Investig. Drugs* **2017**, *26*, 883–887. [CrossRef] [PubMed]

117. Furqan, M.; Akinleye, A.; Mukhi, N.; Mittal, V.; Chen, Y.; Liu, D. STAT inhibitors for cancer therapy. *J. Hematol. Oncol.* **2013**, *6*, 90. [CrossRef]

118. Barati, N.; Momtazi-Borojeni, A.A.; Majeed, M.; Sahebkar, A. Potential therapeutic effects of curcumin in gastric cancer. *J. Cell. Physiol.* **2019**, *234*, 2317–2328. [CrossRef] [PubMed]

119. Keihanian, F.; Saeidinia, A.; Bagheri, R.K.; Johnston, T.P.; Sahebkar, A. Curcumin, hemostasis, thrombosis, and coagulation. *J. Cell. Physiol.* **2018**, *233*, 4497–4511. [CrossRef]

120. Tabeshpour, J.; Hashemzaei, M.; Sahebkar, A. The regulatory role of curcumin on platelet functions. *J. Cell. Biochem.* **2018**, *119*, 8713–8722. [CrossRef]

121. Zendedel, E.; Butler, A.E.; Atkin, S.L.; Sahebkar, A. Impact of curcumin on sirtuins: A review. *J. Cell. Biochem.* **2018**, *119*, 10291–10300. [CrossRef]

122. Fossey, S.L.; Bear, M.D.; Lin, J.; Li, C.; Schwartz, E.B.; Li, P.-K.; Fuchs, J.R.; Fenger, J.; Kisseberth, W.C.; London, C.A. The novel curcumin analog FLLL32 decreases STAT3 DNA binding activity and expression, and induces apoptosis in oesosarcoma cell lines. *BMC Cancer* **2011**, *11*, 112. [CrossRef]

123. Saydmohammed, M.; Joseph, D.; Syed, V. Curcumin suppresses constitutive activation of STAT-3 by up-regulating protein inhibitor of activated STAT-3 (PIAS-3) in ovarian and endometrial cancer cells. *BMC Cancer* **2011**, *11*, 1581–1588. [CrossRef]

124. Strimpakos, A.S.; Sharma, R.A. Curcumin: Preventive and therapeutic properties in laboratory studies and clinical trials. *Antioxid. Redox Signal.* **2008**, *10*, 511–546. [CrossRef] [PubMed]

125. Weissenberger, J.; Priester, M.; Berneuether, C.; Rakel, S.; Glatzel, M.; Seifert, V.; Kögel, D. Dietary curcumin attenuates glioma growth in a syngeneic mouse model by inhibition of the JAK1, 2/STAT3 signaling pathway. *Clin. Cancer Res.* **2010**, *16*, 5781–5795. [CrossRef] [PubMed]

126. Hahn, Y.-I.; Kim, S.-J.; Choi, B.-Y.; Cho, K.-C.; Bandu, R.; Kim, K.P.; Kim, D.-H.; Kim, W.; Park, J.S.; Han, B.W. Curcumin interacts directly with the Cysteine 259 residue of STAT3 and induces apoptosis in H-Ras transformed human mammary epithelial cells. *Sci. Rep.* **2018**, *8*, 6409. [CrossRef] [PubMed]

127. Ashrafizadeh, M.; Ahmadi, Z. Effects of Statins on Gut Microbiota (Microbiome). *Rev. Clin. Med.* **2019**, *6*, 55–59.

128. Zhou, X.X.; Gao, P.J.; Sun, B.G. Pravastatin attenuates interferon-γ action via modulation of stat1 to prevent aortic atherosclerosis in apolipoprotein e-knockout mice. *Clin. Exp. Pharmacol. Physiol.* **2009**, *36*, 373–379. [CrossRef] [PubMed]

129. Levy, D.E.; Darnell, J., Jr. Signalling: Stats: Transcriptional control and biological impact. *Nat. Rev. Mol. Cell Biol.* **2002**, *3*, 651. [CrossRef]

130. Rondonin, R.; Simoni, D.; Maccesi, M.; Romagnoli, R.; Grimaudo, S.; Pipitone, R.M.; Meli, M.; Cascio, A.; Tolomeo, M. Effects of pimozide derivatives on pSTAT5 in K362 cells. *ChemMedChem* **2017**, *12*, 1183–1190. [CrossRef]

131. Siemasko, K.; Chong, A.S.; Jäck, H.-M.; Gong, H.; Williams, J.W.; Finnegan, A. Inhibition of JAK3 and STAT6 tyrosine phosphorylation by the immunosuppressive drug lefunomide leads to a block in IgG1 production. *J. Immunol.* **1998**, *160*, 1581–1588.

132. Bousquet, J.; Chanez, P.; Lacoste, J.Y.; Barneon, G.; Ghavanian, N.; Enander, I.; Venge, P.; Ahlstedt, S.; Simony-Lafontaine, J.; Godard, P.; et al. Eosinophilic inflammation in asthma. *N. Engl. J. Med.* **1990**, *323*, 1033–1039. [CrossRef]
133. Grünig, G.; Warnock, M.; Wakil, A.E.; Venkayya, R.; Brombacher, F.; Rennick, D.M.; Sheppard, D.; Mohrs, M.; Donaldson, D.D.; Locksley, R.M. Requirement for IL-13 independently of IL-4 in experimental asthma. *Science* **1998**, *282*, 2261–2263. [CrossRef] [PubMed]

134. Roche, W.; Williams, J.; Beasley, R.; Holgate, S. Subepithelial fibrosis in the bronchi of asthmatics. *Lancet* **1989**, *333*, 520–524. [CrossRef]

135. Wills-Karp, M.; Luyimbazi, J.; Xu, X.; Schofield, B.; Neben, T.Y.; Karp, C.L.; Donaldson, D.D. Interleukin-13: Central mediator of allergic asthma. *Science* **1998**, *282*, 2258–2261. [CrossRef] [PubMed]

136. Nakano, T.; Inoue, H.; Fukuyama, S.; Matsumoto, K.; Matsumura, M.; Tsuda, M.; Matsumoto, T.; Aizawa, H.; Nakaniishi, Y. Niflumic acid suppresses interleukin-13–induced asthma phenotypes. *Am. J. Respir. Crit. Care Med.* **2006**, *173*, 1216–1221. [CrossRef] [PubMed]

137. Sadeghi, S.; Davoodvandi, A.; Pourhanifeh, M.H.; Sharifi, N.; ArefNezhad, R.; Sahebnasagh, R.; Moghadam, S.A.; Sahebkar, A.; Mirzaei, H. Anti-cancer effects of cinnamon: Insights into its apoptosis effects. *Eur. J. Med. Chem.* **2019**, *178*, 131–140. [CrossRef]

138. Lee, B.-J.; Kim, Y.-J.; Cho, D.-H.; Sohn, N.-W.; Kang, H. Immunomodulatory effect of water extract of cinnamon on anti-CD3-induced cytokine responses and p38, JNK, ERK1/2, and STAT4 activation. *Immunopharmacol. Immunotoxicol.* **2011**, *33*, 714–722. [CrossRef] [PubMed]

139. Romagnoli, R.; Baraldi, P.G.; Prencipe, F.; Lopez-Cara, C.; Rondonin, R.; Simonni, D.; Hamel, E.; Grimaudo, S.; Pipitone, R.M.; Meli, M. Novel iodoacetamido benzoheterocyclic derivatives with potent antileukemic activity are inhibitors of STAT5 phosphorylation. *Eur. J. Med. Chem.* **2016**, *108*, 39–52. [CrossRef]

140. Schafranek, L.; Nievergall, E.; Powell, J.; Hiwase, D.; Leclercq, T.; Hughes, T.; White, D. Sustained inhibition of STAT5, but not JAK2, is essential for TKI-induced cell death in chronic myeloid leukemia. *Leukemia* **2015**, *29*, 76–85. [CrossRef] [PubMed]

141. Rzymski, T.; Mikula, M.; Żylikiewicz, E.; Dreas, A.; Wójcik, K.; Golas, A.; Wójcik, K.; Masiejczyk, M.; Wróbel, A.; Dolata, I. SEL120-34A is a novel CDK8 inhibitor active in AML cells with high levels of serine phosphorylation of STAT1 and STAT5 transactivation domains. *OncoTarget* **2017**, *8*, 33779–33795. [CrossRef]

142. Peter, B.; Bibi, S.; Eisenwort, G.; Wingelhofer, B.; Berger, D.; Stefanzl, G.; Blatt, K.; Herrmann, H.; Hadzijusufovic, E.; Hoermann, G. Drug-induced inhibition of phosphorylation of STAT5 overrides drug resistance in neoplastic mast cells. *Leukemia* **2018**, *32*, 1016–1022. [CrossRef]

143. Simpson, H.M.; Furusawa, A.; Sadashiviah, K.; Civin, C.I.; Banerjee, A. STAT5 inhibition induces TRAIL/DR4 dependent apoptosis in peripheral T-cell lymphoma. *Oncotarget* **2018**, *9*, 16792–16806. [CrossRef] [PubMed]

144. Faderl, S.; Ferrajoli, A.; Harris, D.; Van, Q.; Kantarjian, H.M.; Estrov, Z. Atiprimod blocks phosphorylation of JAK-STAT and inhibits proliferation of acute myeloid leukemia (AML) cells. *Leuk. Res.* **2007**, *31*, 91–95. [CrossRef] [PubMed]

145. Shi, Z.; Zhou, Q.; Gao, S.; Li, W.; Li, X.; Liu, Z.; Jin, P.; Jiang, J. Silibinin inhibits endometrial carcinoma via blocking pathways of STAT3 activation and SREBP1-mediated lipid accumulation. *Lifesci.* **2019**, *29*, 70–80. [CrossRef] [PubMed]

146. Granato, M.; Rizzello, C.; Montani, M.S.G.; Cuomo, L.; Vitillo, M.; Santarelli, R.; Gonnella, R.; D’Orazio, G.; Faggioni, A.; Cironi, M. Quercetin induces apoptosis and autophagy in primary effusion lymphoma cells by inhibiting PI3K/AKT/mTOR and STAT3 signaling pathways. *J. Nutr. Biochem.* **2017**, *41*, 124–136. [CrossRef] [PubMed]

147. Sun, S.; Zhang, X.; Xu, M.; Zhang, F.; Tian, F.; Cui, J.; Xia, Y.; Liang, C.; Zhou, S.; Wei, H. Berberine downregulates CDC6 and inhibits proliferation via targeting JAK-STAT3 signaling in keratinocytes. *Cell Death Dis.* **2019**, *10*, 274. [CrossRef] [PubMed]

148. Oz, B.; Yildirim, A.; Yolbas, S.; Celik, Z.B.; Etem, E.O.; Deniz, G.; Akın, M.; Akar, Z.A.; Karatas, A.; Koca, S.S. Resveratrol inhibits Src tyrosine kinase, STAT3, and Wnt signaling pathway in collagen induced arthritis model. *BioFactors* **2019**, *45*, 69–74. [CrossRef]

149. Su, D.; Gao, Y.-Q.; Dai, W.-B.; Hu, Y.; Wu, Y.-F.; Mei, Q.-X. Helicteric acid, oleanic acid, and betulinic acid, three triterpenes from *Helicteres angustifolia* L., inhibit proliferation and induce apoptosis in HT-29 colorectal cancer cells. *Evid. Based Complement. Altern. Med.* **2017**, 2017, 5180707. [CrossRef] [PubMed]

150. Pandey, M.K.; Sung, B.; Ahn, K.S.; Aggarwal, B.B. Butein suppresses constitutive and inducible signal transducer and activator of transcription (STAT) 3 activation and STAT3-regulated gene products through the induction of a protein tyrosine phosphatase SHP-1. *Mol. Pharmacol.* **2009**, *75*, 525–533. [CrossRef] [PubMed]
151. Agilan, B.; Rajendra Prasad, N.; Kanimozhi, G.; Karthikeyan, R.; Ganesan, M.; Mohana, S.; Velmurugan, D.; Ananthakrishnan, D. Caffeic Acid Inhibits Chronic UVB-Induced Cellular Proliferation Through JAK-STAT3 Signaling in Mouse Skin. Photochem. Photobiol. 2016, 92, 467–474. [CrossRef]

152. Jung, J.E.; Kim, H.S.; Lee, C.S.; Park, D.-H.; Kim, Y.-N.; Lee, M.-J.; Lee, J.W.; Park, J.-W.; Kim, M.-S.; Ye, S.K. Caffeic acid and its synthetic derivative CADPE suppress tumor angiogenesis by blocking STAT3-mediated VEGF expression in human renal carcinoma cells. Carcinogenesis 2007, 28, 1780–1787. [CrossRef]

153. Bhutani, M.; Pathak, A.K.; Nair, A.S.; Kunnumakkara, A.B.; Guha, S.; Sethi, G.; Aggarwal, B.B. Capsaicin is a novel blocker of constitutive and interleukin-6–inducible STAT3 activation. Clin. Cancer Res. 2007, 13, 3024–3032. [CrossRef] [PubMed]

154. Rajendran, P.; Li, F.; Shanmugam, M.K.; Kannaiyan, R.; Goh, J.N.; Wong, K.F.; Wang, W.; Khin, E.; Tergaonkar, V.; Kumar, A.P. Celastrol suppresses growth and induces apoptosis of human hepatocellular carcinoma through the modulation of STAT3/JAK2 signaling cascade in vitro and in vivo. Cancer Prev. Res. 2012, 5, 631–643. [CrossRef] [PubMed]

155. Ma, W.; Xiang, Y.; Yang, R.; Zhang, T.; Xu, J.; Wu, Y.; Liu, X.; Xiang, K.; Zhao, H.; Liu, Y. Cucurbitacin B induces inhibitory effects via the CIP2A/PP2A/C-KIT signaling axis in t (8; 21) acute myeloid leukemia. J. Pharmacol. Sci. 2019, 139, 304–310. [CrossRef] [PubMed]

156. Li, F.; Fernandez, P.P.; Rajendran, P.; Shanmugam, M.K.; Kannaiyan, R.; Goh, J.N.; Wong, K.F.; Wang, W.; Khin, E.; Tergaonkar, V.; Kumar, A.P. Celastrol suppresses growth and induces apoptosis of human hepatocellular carcinoma cells. Cancer Lett. 2010, 292, 197–207. [CrossRef] [PubMed]

157. Ahn, K.S.; Sethi, G.; Sung, B.; Goel, A.; Rahlan, R.; Aggarwal, B.B. Guggulsterone, a farnesoid X receptor antagonist, inhibits constitutive and inducible STAT3 activation through induction of a protein tyrosine phosphatase SHP-1. Cancer Res. 2008, 68, 4406–4415. [CrossRef] [PubMed]

158. Sengupta, S.; Nagalingam, A.; Muniraj, N.; Bonner, M.; Mistriotis, P.; Athinos, A.; Kuppusamy, P.; Lanoue, D.; Cho, S.; Korangath, P. Activation of tumor suppressor LKB1 by honokiol abrogates cancer stem-like phenotype in breast cancer via inhibition of oncogenic Stat3. Oncogene 2017, 36, 5709. [CrossRef] [PubMed]

159. Haridas, V.; Nishimura, G.; Xu, Z.-X.; Connolly, F.; Hanausek, M.; Walaszek, Z.; Zoltaszek, R.; Gutterman, J.U. Hematol. Oncol. 2017, 28, 467–474. [CrossRef] [PubMed]

160. Song, H.; Jung, J.I.; Cho, H.J.; Her, S.; Kwon, S.-H.; Yu, R.; Kang, Y.-H.; Lee, K.W.; Park, J.H.Y. Inhibition of tumor progression by oral piceatannol in mouse 4T1 mammary cancer is associated with decreased angiogenesis and macrophage infiltration. J. Nutr. Biochem. 2015, 26, 1368–1378. [CrossRef]

161. Tahara, T.; Streit, U.; Polish, H.E.; Shair, M.D. STAT3 inhibitory activity of structurally simplified withaferin A analogues. Org. Lett. 2017, 19, 1538–1541. [CrossRef]

162. Subramaniam, A.; Shanmugam, M.K.; Ong, T.H.; Li, F.; Perumal, E.; Chen, L.; Vali, S.; Abbasi, T.; Kapoor, S.; Ahn, K.S. Emodin inhibits growth and induces apoptosis in an orthotopic hepatocellular carcinoma model by blocking activation of STAT3. Br. J. Pharmacol. 2013, 170, 807–821. [CrossRef]

163. Vogel, E.; Santos, D.; Mingels, L.; Verdonckt, T.-W.; Broeck, J.V. RNA interference in insects: Protecting beneficials and controlling pests. Front. Physiol. 2018, 9, 1912. [CrossRef] [PubMed]

164. Siomi, H.; Siomi, M.C. On the road to reading the RNA-interference code. Nature 2009, 457, 396. [CrossRef] [PubMed]

165. Linder, B.; Weirauch, U.; Ewe, A.; Uhlmann, A.; Seifert, V.; Mittelbronn, M.; Harter, P.N.; Aigner, A.; Kögel, D. Therapeutic Targeting of Stat3 Using Lipopolyplex Nanoparticle-Formulated siRNA in a Syngeneic Orthotopic Mouse Glioma Model. Cancers 2019, 11, 333. [CrossRef] [PubMed]

166. Gao, L.-F.; Wen, L.-J.; Hu, Y;; Zhang, L.-Y.; Meng, Y.; Shao, Y.-T.; Xu, D.-Q.; Zhao, X.-J. Knockdown of Stat3 expression using RNAi inhibits growth of laryngeal tumors in vivo. Acta Pharmacol. Sin. 2006, 27, 347. [CrossRef]

167. Gao, Z.; Huang, C.; Qiu, Z.; Jiang, T.; Zhu, L.; Cao, J.; Zhang, F.; Huang, K. Effect of RNAi-mediated STAT3 gene inhibition on metastasis of human pancreatic cancer cells. Zhonghua Wai Ke Za Zhi 2008, 46, 1010–1013. [PubMed]

168. Kaymaz, B.T.; Selvi, N.; Gündüz, C.; Aktan, Ç.; Dalmizrak, A.; Saydam, G.; Kosova, B. Repression of STAT3, STAT5A, and STAT5B expressions in chronic myelogenous leukemia cell line K-562 with unmodified or chemically modified siRNAs and induction of apoptosis. Anna. Hematol. 2013, 92, 151–162. [CrossRef] [PubMed]
169. Konnikova, L.; Kotecki, M.; Kruger, M.M.; Cochran, B.H. Knockdown of STAT3 expression by RNAi induces apoptosis in astrocytoma cells. *BMC Cancer* 2003, 3, 23. [CrossRef]

170. Furnari, F.B.; Fenton, T.; Bachoo, R.M.; Mukasa, A.; Stommel, J.M.; Stegh, A.; Hahn, W.C.; Ligon, K.L.; Louis, D.N.; Brennan, C. Malignant astrocytic glioma: Genetics, biology, and paths to treatment. *Genes Dev.* 2007, 21, 2683–2710. [CrossRef] [PubMed]

171. Altaner, C. Glioblastoma and stem cells-Minireview. *Neoplasma* 2008, 55, 369.

172. Das, S.; Srikanth, M.; Kessler, J.A. Cancer stem cells and glioma. *Nat. Rev. Neurol.* 2008, 4, 427. [CrossRef]

173. Singh, S.K.; Clarke, I.D.; Terasaki, M.; Bonn, V.E.; Hawkins, C.; Squire, J.; Dirks, P.B. Identification of a cancer stem cell in human brain tumors. *Cancer Res.* 2003, 63, 5821–5828. [PubMed]

174. Yuan, X.; Curtin, J.; Xiong, Y.; Liu, G.; Waschsmann-Hogiu, S.; Farkas, D.L.; Black, K.L.; John, S.Y. Isolation of cancer stem cells from adult glioblastoma multiforme. *Oncogene* 2004, 23, 9392. [CrossRef] [PubMed]

175. Li, G.-H.; Wei, H.; Lv, S.-Q.; Ji, H.; Wang, D.-L. Knockdown of STAT3 expression by RNAi suppresses cell growth and induces apoptosis and differentiation in glioblastoma stem cells. *Int. J. Oncol.* 2010, 37, 103–110. [PubMed]

176. Yuan, X.; Curtin, J.; Xiong, Y.; Liu, G.; Waschsmann-Hogiu, S.; Farkas, D.L.; Black, K.L.; John, S.Y. Isolation of cancer stem cells from adult glioblastoma multiforme. *Oncogene* 2004, 23, 9392. [CrossRef] [PubMed]

177. Wang, H.; Li, X.; Lu, X. Silencing of signal transducer and activator of transcription 3 gene expression using RNAi enhances the efficacy of radiotherapy for laryngeal carcinoma in vivo. Zhonghua Er Bi Yan Hou Tong Ke Za Zhi 2009, 44, 591–596. [PubMed]

178. Das, S.; Srikanth, M.; Kessler, J.A. Cancer stem cells and glioma. *Nat. Rev. Neurol.* 2008, 4, 427. [CrossRef]

179. Siegel, R.L.; Miller, K.D.; Jemal, A. Cancer statistics, 2019. *CA Cancer J. Clin.* 2019, 69, 7–34. [CrossRef] [PubMed]

180. Ashrafizadeh, M.; Ahmadi, Z.; Mohammadinejad, R.; Kaviyani, N.; Tavakol, S. Monoterpenes modulating autophagy: A review study. *Basic Clin. Pharmacol. Toxicol.* 2019. [CrossRef] [PubMed]

181. Do, T.N.T.; Lee, W.-H.; Loo, C.-Y.; Zavgorodniy, A.V.; Rohanizadeh, R. Hydroxyapatite nanoparticles as vectors for gene delivery. *Ther. Deliv.* 2012, 3, 623–632.

182. Bose, S.; Tarafder, S. Calcium phosphate ceramic systems in growth factor and drug delivery for bone tissue engineering: A review. *Biomaterials.* 2012, 8, 1401–1421. [CrossRef]

183. Olton, D.; Li, J.; Wilson, M.E.; Rogers, T.; Close, J.; Huang, L.; Kumta, P.N.; Sfeir, C. Nanostructured calcium phosphates (NanoCaPs) for non-viral gene delivery: Influence of the synthesis parameters on transfection efficiency. *Biomaterials* 2007, 28, 1267–1279. [CrossRef] [PubMed]

184. Liang, Z.; Wang, H.; Guo, B.; Li, F.; Liu, J.; Liu, Z.; Xu, L.; Yun, W.; Zhao, X.; Zhang, L. Inhibition of prostate cancer RM1 cell growth in vitro by hydroxyapatite nanoparticle-delivered short hairpin RNAs against Stat3. *Mol. Med. Rep.* 2017, 16, 459–465. [CrossRef] [PubMed]

185. Jia, X.; Zhang, X.; Xue, X.; Shen, L.; Yao, Y.; Yang, Z.; Liu, P. STAT3 decoy oligodeoxynucleotides-loaded solid lipid nanoparticles induce cell death and inhibit invasion in ovarian cancer cells. *PLoS ONE* 2015, 10, e0124924. [CrossRef]

186. Kotmakçı, M.; Çetinta¸s, V.B.; Kantarcı, A.G. Preparation and characterization of lipid nanoparticle complexes for STAT3 downregulation and overcoming chemotherapy resistance in lung cancer cells. *Int. J. Pharm.* 2017, 525, 101–111. [CrossRef] [PubMed]

187. Pindiprolu, S.K.S.; Krishnamurthy, P.T.; Chintamaneni, P.K. Pharmacological targets of breast cancer stem cells: A review. *Naunyn Schmiedebergs Arch. Pharmacol.* 2018, 391, 463–479. [CrossRef] [PubMed]

188. Li, R.; You, S.; Hu, Z.; Chen, Z.G.; Sica, G.L.; Khuri, F.R.; Curran, W.J.; Shin, D.M.; Deng, X. Inhibition of STAT3 by niclosamide synergizes with erlotinib against head and neck cancer. *PLoS ONE* 2013, 8, e74670. [CrossRef] [PubMed]

189. Ma, Y.; Zhang, X.; Xu, X.; Shen, L.; Yao, Y.; Yang, Z.; Liu, P. STAT3 decoy oligodeoxynucleotides-loaded solid lipid nanoparticles induce cell death and inhibit invasion in ovarian cancer cells. *PLoS ONE* 2015, 10, e0124924. [CrossRef]

190. Kim, S.H.; Yoo, H.S.; Joo, M.K.; Kim, T.; Park, J.-J.; Lee, B.J.; Chun, H.J.; Lee, S.W.; Bak, Y.-T. Arsenic trioxide attenuates STAT-3 activity and epithelial-mesenchymal transition through induction of SHP-1 in gastric cancer cells. *BMC Cancer* 2018, 18, 150. [CrossRef]
191. Zhu, L.; Cheng, X.; Shi, J.; Lin, J.; Chen, G.; Jin, H.; Liu, A.B.; Pyo, H.; Ye, J.; Zhu, Y. Crossstalk between bone marrow-derived myofibroblasts and gastric cancer cells regulates cancer stemness and promotes tumorigenesis. *Oncoogene* 2016, 35, 5388. [CrossRef]

192. Chang, J.C. Cancer stem cells: Role in tumor growth, recurrence, metastasis, and treatment resistance. *Medicine* 2016, 95. [CrossRef]

193. Su, W.-P.; Cheng, F.-Y.; Shieh, D.-B.; Yeh, C.-S.; Su, W.-C. PLGA nanoparticles codeliver paclitaxel and Stat3 siRNA to overcome cellular resistance in lung cancer cells. *Int. J. Nanomed.* 2012, 7, 4269. [CrossRef]

194. Molavi, O.; Mahmud, A.; Hamdy, S.; Hung, R.W.; Lai, R.; Samuel, J.; Lavasanifar, A. Development of a poly (d, l-lactic-co-glycolic acid) nanoparticle formulation of STAT3 inhibitor JSI-124: Implication for cancer immunotherapy. *Mol. Pharm.* 2010, 7, 364–374. [CrossRef] [PubMed]

195. Su, W.-P.; Cheng, F.-Y.; Shieh, D.-B.; Yeh, C.-S.; Su, W.-C. PLGA nanoparticles codeliver paclitaxel and Stat3 siRNA to overcome cellular resistance in lung cancer cells. *Int. J. Nanomed.* 2012, 7, 4269. [CrossRef]

196. Beum, P.V.; Lindorfer, M.A.; Peek, E.M.; Stukenberg, P.T.; de Weers, M.; Beurskens, F.J.; Parren, P.W.; van de Winkel, J.G.; Taylor, R.P. Penetration of antibody-opsonized cells by the membrane attack complex of complement promotes Ca2+ influx and induces streamers. *Eur. J. Immunol.* 2011, 41, 2436–2446. [CrossRef] [PubMed]

197. de la Puente, P.; Luderer, M.J.; Federico, C.; Jin, A.; Gilson, R.C.; Egbulefu, C.; Alhallak, K.; Shah, S.; Muz, B.; Sun, J. Enhancing proteasome-inhibitory activity and specificity of bortezomib by CD38 targeted nanoparticles in multiple myeloma. *J. Control. Release* 2018, 270, 158–176. [CrossRef]

198. Schlosser, E.; Mueller, M.; Fischer, S.; Basta, S.; Busch, D.H.; Gander, B.; Groettrup, M. TLR ligands and cell vaccine delivery to dendritic cells. *Vaccine* 2005, 23, 3588–3600. [CrossRef] [PubMed]

199. Elamanchili, P.; Lutsiak, C.M.; Hamdy, S.; Diwan, M.; Samuel, J. “Pathogen-mimicking” nanoparticles for vaccine delivery to dendritic cells. *J. Immunother.* 2007, 30, 378–395. [CrossRef]

200. Foged, C.; Sundblad, A.; Hovgaard, L. Targeting vaccines to dendritic cells. *Pharm. Res.* 2002, 19, 229–238. [CrossRef]

201. Jiang, W.; Gupta, R.K.; Deshpande, M.C.; Schwendeman, S.P. Biodegradable poly (lactic-co-glycolic acid) microparticles for injectable delivery of vaccine antigens. *Adv. Drug Deliv. Rev.* 2005, 57, 391–410. [CrossRef]

202. Schlosser, E.; Mueller, M.; Fischer, S.; Basta, S.; Busch, D.H.; Gander, B.; Groettrup, M. TLR ligands and antigen need to be coencapsulated into the same biodegradable microsphere for the generation of potent cytotoxic T lymphocyte responses. *Vaccine* 2008, 26, 1626–1637. [CrossRef]

203. Waeckerle-Men, Y.; Gander, B.; Groettrup, M. Delivery of tumor antigens to dendritic cells using biodegradable microspheres. In *Adaptive Immunotherapy: Methods and Protocols*; Springer: Berlin, Germany, 2005; pp. 35–46.

204. Waeckerle-Men, Y.; Gander, B.; Groettrup, M. PLGA microspheres for improved antigen delivery to dendritic cells as cellular vaccines. *Adv. Drug Deliv. Rev.* 2005, 57, 475–482. [CrossRef] [PubMed]

205. Molavi, O.; Mahmud, A.; Hamdy, S.; Hung, R.W.; Lai, R.; Samuel, J.; Lavasanifar, A. Development of a poly (d, l-lactic-co-glycolic acid) nanoparticle formulation of STAT3 inhibitor JSI-124: Implication for cancer immunotherapy. *Mol. Pharm.* 2010, 7, 364–374. [CrossRef] [PubMed]
210. Shain, A.H.; Bastian, B.C. From melanocytes to melanomas. *Nat. Rev. Cancer* 2016, 16, 345. [CrossRef] [PubMed]
211. Maverakis, E.; Cornelius, L.A.; Bowen, G.M.; Phan, T.; Patel, F.B.; Fitzmaurice, S.; He, Y.; Burrall, B.; Duong, C.; Kloxin, A.M. Metastatic melanoma—a review of current and future treatment options. *Acta Derm. Venereol.* 2015, 95, 516–527. [CrossRef]
212. Labala, S.; Jose, A.; Chawla, S.R.; Khan, M.S.; Bhatnagar, S.; Kulkarni, O.P.; Venuganti, V.V.K. Effective melanoma cancer suppression by iontophoretic co-delivery of STAT3 siRNA and imatinib using gold nanoparticles. *Int. J. Pharm.* 2017, 525, 407–417. [CrossRef] [PubMed]
213. Song, J.; Shi, J.; Dong, D.; Fang, M.; Zhong, W.; Wang, K.; Wu, N.; Huang, Y.; Liu, Z.; Cheng, Y. A new approach to predict progression-free survival in stage IV EGFR-mutant NSCLC patients with EGFR-TKI therapy. *Clin. Cancer Res.* 2018, 24, 3583–3592. [CrossRef]
214. Gazdar, A. Activating and resistance mutations of EGFR in non-small-cell lung cancer: Role in clinical response to EGFR tyrosine kinase inhibitors. *Oncogene* 2009, 28, S24. [CrossRef] [PubMed]
215. Pardanani, A.; Harrison, C.; Cortes, J.E.; Cervantes, F.; Mesa, R.A.; Masszi, T.; Mishchenko, E.; Jourdan, E.; Vannucchi, A.M. Safety and efficacy of fedratinib in patients with primary or secondary myelofibrosis: A randomized clinical trial. *JAMA Oncol.* 2015, 1, 643–651. [CrossRef] [PubMed]
216. Chen, D.; Zhang, F.; Wang, J.; He, H.; Duan, S.; Zhu, R.; Chen, C.; Chen, Y.; Yin, L. Biodegradable Nanoparticles Mediated Co-Delivery of Erolitinib (ELTN) and Fedratinib (FDTN) toward the Treatment of ELTN-Resistant Non-Small Cell Lung Cancer (NSCLC) via Suppression of the JAK2/STAT3 Signaling Pathway. *Front. Pharmacol.* 2018, 9, 1214. [CrossRef] [PubMed]
217. Hornez, J.-C.; Chai, F.; Monchau, F.; Blanchemain, N.; Descamps, M.; Hildebrand, H. Biological and physico-chemical assessment of hydroxyapatite (HA) with different porosity. *Biomol. Eng.* 2007, 24, 505–509. [CrossRef] [PubMed]
218. Kumar, G.S.; Girija, E.; Thamizhavel, A.; Yokogawa, Y.; Kalkura, S.N. Synthesis and characterization of bioactive hydroxyapatite–calcite nanocomposite for biomedical applications. *J. Colloid Interface Sci.* 2010, 349, 56–62. [CrossRef] [PubMed]
219. Levy-Nissenbaum, E.; Radovic-Moreno, A.F.; Wang, A.Z.; Langer, R.; Farokhzad, O.C. Nanotechnology and aptamers: Applications in drug delivery. *Trends Biotechnol.* 2008, 26, 442–449. [CrossRef] [PubMed]
220. McAllister, K.; Sazani, P.; Adam, M.; Cho, M.J.; Rubinstein, M.; Samulski, R.J.; DeSimone, J.M. Polymeric nanogels produced via inverse microemulsion polymerization as potential gene and antisense delivery agents. *J. Am. Chem. Soc.* 2002, 124, 15198–15207. [CrossRef] [PubMed]
221. Shi, Z.; Huang, X.; Cai, Y.; Tang, R.; Yang, D. Size effect of hydroxyapatite nanoparticles on proliferation and apoptosis of osteoblast-like cells. *Acta Biomater.* 2009, 5, 338–345. [CrossRef]
222. Sun, H.; Jiang, M.; Zhu, S. In vitro and in vivo studies on hydroxyapatite nanoparticles as a novel vector for inner ear gene therapy. *Zhonghua Er Bi Yan Hou Tou Jing Wai Ke Za Zhi* 2008, 43, 51–57.
223. Ye, F.; Guo, H.; Zhang, H.; He, X. Polymeric micelle-templated synthesis of hydroxyapatite hollow nanoparticles for a drug delivery system. *Acta Biomater.* 2010, 6, 2212–2218. [CrossRef]
224. Liang, Z.W.; Guo, B.F.; Li, Y.; Li, X.J.; Li, X.; Zhao, L.J.; Gao, L.F.; Yu, H.; Zhao, X.J.; Zhang, L.; et al. Plasmid-based Stat3 siRNA delivered by hydroxyapatite nanoparticles suppresses mouse prostate tumour growth in vivo. *Asian J. Androl.* 2011, 13, 481–486. [CrossRef] [PubMed]
225. Behlke, M.A. Progress towards in vivo use of siRNAs. *Mol. Ther.* 2006, 13, 644–670. [CrossRef]
226. Demeneix, B.; Behr, J.P. Polyethyleneimine (PEI). *Adv. Genet.* 2005, 53, 215–230.
227. Doody, A.; Putnam, D. RNA-interference effectors and their delivery. *Crit. Rev. Ther. Drug Carr. Syst.* 2006, 23, 137–164.
228. Uprichard, S.L. The therapeutic potential of RNA interference. *FEBS Lett.* 2005, 579, 5996–6007. [CrossRef]
229. Alshamsan, A.; Hamdy, S.; Samuel, J.; El-Kadi, A.O.; Lavasanifar, A.; Uludağ, H. The induction of tumor apoptosis in B16 melanoma following STAT3 siRNA delivery with a lipid-substituted polyethyleneimine. *Biomaterials* 2010, 31, 1420–1428. [CrossRef]
230. Liu, C.; Li, X.-W.; Cui, L.-M.; Li, L.-C.; Chen, L.-Y.; Zhang, X.-W. Inhibition of tumor angiogenesis by TTF1 from extract of herbal medicine. *World J. Gastroenterol.* WJG 2011, 17, 4875. [CrossRef] [PubMed]
231. Li, Y.; Bian, L.; Cui, F.; Li, L.; Zhang, X. TTF1-induced apoptosis of HepG2 cells through a mitochondrial pathway. *Oncol. Rep.* 2011, 26, 651–657.
232. Li, Y.; Cui, F.; Zhang, X. Preparation technology of Sorbaria sorbifolia solid lipid nanoparticles. *Lishizhen Med. Mater. Med. Res.* 2012, 23, 2549–2550.

233. Xiao, B.; Lin, D.; Zhang, X.; Zhang, M.; Zhang, X. TTF1, in the form of nanoparticles, inhibits angiogenesis, cell migration and cell invasion in vitro and in vivo in human hepatoma through STAT3 regulation. *Molecules* 2016, 21, 1507. [CrossRef]

234. Kajimoto, K.; Yamamoto, M.; Watanabe, M.; Kigasawa, K.; Kanamura, K.; Harashima, H.; Kogure, K. Noninvasive and persistent transfollicular drug delivery system using a combination of liposomes and iontophoresis. *Int. J. Pharm.* 2011, 403, 57–65. [CrossRef] [PubMed]

235. Han, I.; Kim, M.; Kim, J. Enhanced transfollicular delivery of Adriamycin with a liposome and iontophoresis. *Exp. Dermatol.* 2004, 13, 86–92. [CrossRef] [PubMed]

236. Paudel, K.S.; Milewski, M.; Swadley, C.L.; Brogden, N.K.; Ghosh, P.; Stinchcomb, A.L. Challenges and opportunities in dermal/transdermal delivery. *Ther. Deliv.* 2010, 1, 109–131. [CrossRef] [PubMed]

237. Souza, J.G.; Dias, K.; Pereira, T.A.; Bernardi, D.S.; Lopez, R.F. Topical delivery of ocular therapeutics: Carrier systems and physical methods. *J. Pharm. Pharmacol.* 2014, 66, 507–530. [CrossRef] [PubMed]

238. Jose, A.; Labala, S.; Ninave, K.M.; Gade, S.K.; Venuganti, V.V.K. Efficacy of anti-STAT3 siRNA by transdermal delivery and combined iontophoresis for cutaneous diseases. *Mater. Med. Res.* 2018, 25, 2549–2550. [CrossRef]

239. Han, I.; Kim, M.; Kim, J. Enhanced transfollicular delivery of Adriamycin with a liposome and iontophoresis. *Exp. Dermatol.* 2004, 13, 86–92. [CrossRef] [PubMed]

240. Eljarrat-Binstock, E.; Orucov, F.; Aldouby, Y.; Frucht-Pery, J.; Domb, A.J. Charged nanoparticles delivery to the eye using hydrogel iontophoresis. *J. Control. Release* 2008, 126, 156–161. [CrossRef] [PubMed]

241. Jose, A.; Labala, S.; Venuganti, V.V.K. Co-delivery of curcumin and STAT3 siRNA using deformable cationic liposomes to treat skin cancer. *J. Drug Target.* 2017, 25, 330–341. [CrossRef]

242. Jose, A.; Labala, S.; Ninave, K.M.; Gade, S.K.; Venuganti, V.V.K. Effective skin cancer treatment by topical co-delivery of curcumin and STAT3 siRNA using cationic liposomes. *AAPS PharmSciTech* 2018, 19, 166–175. [CrossRef]

243. Noy, R.; Pollard, J.W. Tumor-associated macrophages: From mechanisms to therapy. *Immunity* 2014, 41, 49–61. [CrossRef]

244. Andersen, M.N.; Etzerodt, A.; Graversen, J.H.; Holthof, L.C.; Moestrup, S.K.; Hokland, M.; Möller, H.J. STAT3 inhibition specifically in human monocytes and macrophages by CD163-targeted corosolic acid-containing liposomes. *Cancer Immunol. Immunother.* 2019, 68, 489–502. [CrossRef] [PubMed]

245. Yang, M.; McKay, D.; Pollard, J.W.; Lewis, C.E. Diverse functions of macrophages in different tumor microenvironments. *Cancer Res.* 2018, 78, 5492–5503. [CrossRef] [PubMed]

246. Zheng, Q.-W.; Liu, L.; Gong, C.-Y.; Shi, H.-S.; Zeng, Y.-H.; Wang, X.-Z.; Zhao, Y.-W.; Wei, Y.-Q. Prognostic significance of tumor-associated macrophages in solid tumor: A meta-analysis of the literature. *PLoS ONE* 2012, 7, e50946. [CrossRef] [PubMed]

247. Cheng, F.; Wang, H.-W.; Cuenca, A.; Huang, M.; Ghansah, T.; Brayer, J.; Kerr, W.G.; Takeda, K.; Akira, S.; Schoenberger, S.P. A critical role for Stat3 signaling in immune tolerance. *Immunity* 2003, 19, 425–436. [CrossRef]

248. Zhang, L.; Alizadeh, D.; Van Handel, M.; Kortylewski, M.; Yu, H.; Badie, B. Stat3 inhibition activates tumor macrophages and abrogates glioma growth in mice. *Glia* 2009, 57, 1458–1467. [CrossRef] [PubMed]

249. Kortylewski, M.; Kuwahara, K.; Wang, T.; Wei, S.; Zhang, S.; Pilon-Thomas, S.; Niu, G.; Kay, H.; Mulé, J.; Kerr, W.G. Inhibiting Stat3 signaling in the hematopoietic system elicits multicomponent antitumor immunity. *Nat. Med.* 2005, 11, 1314. [CrossRef] [PubMed]

250. Herrmann, A.; Kortylewski, M.; Kuwahara, K.; Zhang, C.; Reckamp, K.; Armstrong, B.; Wang, L.; Kowolik, C.; Deng, J.; Figlin, R. Targeting Stat3 in the myeloid compartment drastically improves the in vivo antitumor functions of adoptively transferred T cells. *Cancer Res.* 2010, 70, 7455–7464. [CrossRef]

251. Giurisato, E.; Xu, Q.; Lonardi, S.; Telfer, B.; Russo, I.; Pearson, A.; Finegan, K.G.; Wang, W.; Wang, J.; Gray, N.S. Myeloid ERK5 deficiency suppresses tumor growth by blocking protumor macrophage polarization via STAT3 inhibition. *Proc. Natl. Acad. Sci. USA* 2018, 115, E2801–E2810. [CrossRef]

252. Bader, H.; Ringsdorf, H.; Schmidt, B. Water-soluble polymers in medi cine. *Angew. Makromol. Chem.* 1984, 123, 457–485. [CrossRef]
Cells 2019, 8, 1158

254. Jones, M.-C.; Leroux, J.-C. Polymeric micelles—A new generation of colloidal drug carriers. Eur. J. Pharm. Biopharm. 1999, 48, 101–111. [CrossRef]

255. Kwon, G.S.; Forrest, M.L. Amphiphilic block copolymer micelles for nanoscale drug delivery. Drug Dev. Res. 2006, 67, 15–22. [CrossRef]

256. Lu, Y.; Park, K. Polymeric micelles and alternative nanonized delivery vehicles for poorly soluble drugs. Int. J. Pharm. 2013, 453, 198–214. [CrossRef] [PubMed]

257. Matsumura, Y.; Maeda, H. A new concept for macromolecular therapeutics in cancer chemotherapy: Mechanism of tumor-tropic accumulation of proteins and the antitumor agent smans. Cancer Res. 1986, 46, 6387–6392. [PubMed]

258. Maeda, H.; Tsukigawa, K.; Fang, J. A Retrospective 30 Years After Discovery of the Enhanced Permeability and Retention Effect of Solid Tumors: Next-Generation Chemotherapeutics and Photodynamic Therapy—Problems, Solutions, and Prospects. Microcirculation 2016, 23, 173–182. [CrossRef] [PubMed]

259. Soleimani, A.H.; Garg, S.M.; Paiva, I.M.; Vakili, M.R.; Alshareef, A.; Huang, Y.-H.; Molavi, O.; Lai, R.; Lavasanifar, A. Micellar nano-carriers for the delivery of STAT3 dimerization inhibitors to melanoma. Drug Deliv. Transl. Res. 2017, 7, 571–581. [CrossRef] [PubMed]

260. Molavi, O.; Ma, Z.; Mahmud, A.; Alshareem, A.; Samuel, J.; Lai, R.; Kwon, G.S.; Lavasanifar, A. Polymeric micelles for the solubilization and delivery of STAT3 inhibitor cucurbitacins in solid tumors. Int. J. Pharm. 2008, 347, 118–127. [CrossRef] [PubMed]

261. Luo, Z.; Wang, C.; Yi, H.; Li, P.; Pan, H.; Liu, L.; Cai, L.; Ma, Y. Nanovaccine loaded with poly I: C and STAT3 siRNA robustly elicits anti-tumor immune responses through modulating tumor-associated dendritic cells in vivo. Biomaterials 2015, 38, 50–60. [CrossRef] [PubMed]

262. Jiang, Q.; Dai, L.; Cheng, L.; Chen, X.; Li, Y.; Zhang, S.; Su, X.; Zhao, X.; Wei, Y.; Deng, H. Efficient inhibition of intraperitoneal ovarian cancer growth in nude mice by liposomal delivery of short hairpin RNA against STAT 3. J. Obstet. Gynaecol. Res. 2013, 39, 701–709. [CrossRef] [PubMed]

263. Kopechek, J.A.; Carson, A.R.; McTiernan, C.F.; Chen, X.; Hasjim, B.; Lavery, L.; Sen, M.; Grandis, J.R.; Villanueva, F.S. Ultrasound targeted microbubble destruction-mediated delivery of a transcription factor decoy inhibits STAT3 signaling and tumor growth. Theranostics 2015, 5, 1378. [CrossRef]

264. Shi, K.; Fang, Y.; Gao, S.; Yang, D.; Bi, H.; Xue, J.; Lu, A.; Li, Y.; Ke, L.; Lin, X. Inorganic kernel-Supported asymmetric hybrid vesicles for targeting delivery of STAT3-decoy oligonucleotides to overcome anti-HER2 therapeutic resistance of BT474R. J. Control. Release 2018, 279, 53–68. [CrossRef]

265. Garg, S.M.; Vakili, M.R.; Molavi, O.; Lavasanifar, A. Self-Associating Poly (ethylene oxide)-block-poly (ε-carboxyl-ε-caprolactone) Drug Conjugates for the Delivery of STAT3 Inhibitor JSI-124: Potential Application in Cancer Immunotherapy. Mol. Pharm. 2017, 14, 2570–2584. [CrossRef] [PubMed]

266. Mai, J.; Huang, Y.; Mu, C.; Zhang, G.; Xu, R.; Guo, X.; Xia, X.; Volk, D.E.; Lokesh, G.L.; Thiviyathan, V. Bone marrow endothelium-targeted therapeutics for metastatic breast cancer. J. Control. Release 2014, 184, 22–29. [CrossRef] [PubMed]

267. Falamarzian, A.; Montazeri Aliabadi, H.; Molavi, O.; Seubert, J.M.; Lai, R.; Uludağ, H.; Lavasanifar, A. Effective down-regulation of signal transducer and activator of transcription 3 (STAT3) by polyplexes of siRNA and lipid-substituted polyethyleneimine for sensitization of breast tumor cells to conventional chemotherapy. J. Biomed. Mater. Res. Part A 2014, 102, 3216–3228. [CrossRef] [PubMed]

268. Li, Z.; Guan, Y.-Q.; Liu, J.-M. The role of STAT-6 as a key transcription regulator in HeLa cell death induced by IFN-γ/TNF-a co-immobilized on nanoparticles. Biomaterials 2014, 35, 5016–5027. [CrossRef] [PubMed]

269. Molavi, O.; Ma, Z.; Hamdy, S.; Lavasanifar, A.; Samuel, J. Immunomodulatory and anticancer effects of intra-tumoral co-delivery of synthetic lipid A adjuvant and STAT3 inhibitor, JSI-124. Immunopharmacol. Immunotoxicol. 2009, 31, 214–221. [CrossRef] [PubMed]

270. Pan, J.; Ruan, W.; Qin, M.; Long, Y.; Wan, T.; Yu, K.; Zhai, Y.; Wu, C.; Xu, Y. Intradermal delivery of STAT3 siRNA to treat melanoma via dissolving microneedles. Sci. Rep. 2018, 8, 1117. [CrossRef] [PubMed]

271. Wilhelm, S.; Tavares, A.J.; Dai, Q.; Ohta, S.; Audet, J.; Dvorak, H.F.; Chan, W.C. Analysis of nanoparticle delivery to tumours. Nat. Rev. Mater. 2016, 1, 16014. [CrossRef]

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