Advances in Immunosuppressive Agents Based on Signal Pathway

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Immune abnormality involves in various diseases, such as infection, allergic diseases, autoimmune diseases, as well as transplantation. Several signal pathways have been demonstrated to play a central role in the immune response, including JAK/STAT, NF-κB, PI3K/AKT-mTOR, MAPK, and Keap1/Nrf2/ARE pathway, in which multiple targets have been used to develop immunosuppressive agents. In recent years, varieties of immunosuppressive agents have been approved for clinical use, such as the JAK inhibitor tofacitinib and the mTOR inhibitor everolimus, which have shown good therapeutic effects. Additionally, many immunosuppressive agents are still in clinical trials or preclinical studies. In this review, we classified the immunosuppressive agents according to the immunopharmacological mechanisms, and summarized the phase of immunosuppressive agents.

Keywords: immunosuppressive agent, jak-stat, NF-κB, PI3K-AKT-mTOR, MAPK, Keap1/Nrf2-ARE

INTRODUCTION

Immunosuppressive agents are a class of drugs that inhibit the abnormal immune response of the body and suppress the proliferation and function of cells related to the immune response (macrophages such as T cells and B cells), thereby reducing the antibody immune response, and are now mainly used in organ transplantation anti-rejection reactions and autoimmune diseases. Undoubtedly, immunosuppressive agents have achieved great progress and success in the treatment of these diseases, thus further demonstrating the great research and development prospects of immunosuppressive agents. In 1949, Edward and Philip successfully extracted the adrenocorticotropic hormone cortisone from animals and elucidated its structure and biological effects. Since then, immunosuppressive agents have been on the stage of history, and glucocorticoids have been widely used in clinical practice, and two great scientists were awarded the Nobel Prize in 1950 for this discovery. However, medical problems abound, and the quest of our ancestors never stops. In the 1950s, the anti-rejection reactions present in organ transplants could only be controlled by radiation, and patient survival could not be guaranteed. Subsequently, medical personnel applied glucocorticoids to organ transplants, but the quality of patient survival was delayed due to the highly toxic side effects of hormones, and the development of immunosuppressive agents was imminent. It was not until 1953 when George Hitchings and his associate Gertrude Elion successfully developed the anti-cancer drug 6-mercaptopurine and structurally modified it to develop mercaptopurine, which was used in combination with hormonal drugs for organ transplantation, that the life span of transplanted organs was greatly extended, but research into the use of new drugs for organ transplantation is still progressing at a rapid pace today. Although the problems of organ transplantation have improved, new problems have arisen. We all know that the use of immunosuppressive drugs is a very effective way to treat autoimmune diseases, but the drugs...
used need constant innovation. In the early days, autoimmune diseases were mainly treated with glucocorticoids and cytotoxic drugs, but it was found that these two types of drugs were too selective for cells, thus easily injuring normal cells by mistake. As a result, the demand for highly selective immunosuppressive drugs has gradually increased. Cyclosporine A has received much attention since its successful use in the treatment of organ anti-rejection, and researchers have again used cyclosporine A in animal studies and found it to be effective in human-like autoimmune myasthenia gravis in rats. Since then, cyclosporine A has been used clinically to treat human autoimmune diseases. However, mankind has never stopped for the use of immunosuppressive drugs to treat diseases. In 1992, a neo-coronavirus outbreak was reported in Wuhan, and studies on patients can reveal that granulocyte colony factor, interferon-inducible protein 10, monocyte chemotactic protein 1, macrophage inflammatory protein 1α, and TNF-α levels are higher in patients with severe COVID-19 than in those without severe disease, demonstrating that cytokine storms can have an impact on the extent of COVID-19 disease (Huang et al., 2020). The use of glucocorticoids for the treatment of refractory cytokine storms is now well documented and widely accepted, and researchers have put methylprednisolone into clinical use and found it to be effective in patients with COVID-19, with a mild discontinuation response. But then researchers conducted a retrospective study that included 309 patients with severe MERS and found that glucocorticoids, while suppressing the cytokine storm, also interfered with the immune response, resulting in reduced clearance of the pathogen (Arabi et al., 2018). Therefore, for patients with severe COVID-19, the principle of no glucocorticoid therapy for patients not meeting the indications for glucocorticoid application is currently adopted. Of course, seeing the dawn of immunosuppressive therapy for COVID-19, researchers will devote more time and effort to the development and use of immunosuppressive agents in the future.

Since the successful completion of the first kidney transplantation in the United States in the 1950s, immunosuppression has received more attention. In 1978, cyclosporine A was first used in clinical renal transplantation in the United Kingdom, and its combined application with hormonal drugs and azathioprine was called “triple therapy”, which greatly improved the 1-year survival rate of transplanted kidneys, which was a new milestone in the history of immunosuppressant development, from which immunosuppressive agents began to develop formally in the 1970s. By now, various types of immunosuppressive agents have been put into clinical application, and the immunosuppressive agents commonly used in clinical practice can be broadly classified into the following categories: 1). Glucocorticoids; 2). Cytotoxic drugs (e.g., cyclophosphamide); 3). Calmodulin inhibitors (e.g., cyclosporine, tacrolimus); 4). Macrolamines (e.g., macrodilimus ethyl ester); 5). Chinese herbal immunosuppressive agents (e.g., total ginseng). Glucocorticoids have a wide range of pharmacological mechanisms of action and are the most commonly used immunosuppressive agents in clinical practice, and they can have inhibitory effects on multiple aspects of the immune response. Studies have shown that it inhibits the production of initial T lymphocytes and monocytes mainly by affecting the differentiation maturation, phenotype and function of dendritic cells in order to induce clonal incompetence or apoptosis of T lymphocytes, followed by the acquisition of immune tolerance to specific antigens. However, because of their excessive adverse effects, they are currently used mainly for the combination treatment of various diseases. In order to minimize the adverse effects caused by glucocorticosteroids during treatment, researchers are working to develop new synthetic immunosuppressive agents to reduce the amount of glucocorticosteroids. In the 1960s, azathioprine was successfully modified and first used successfully in organ transplantation (Nordham and Ninokawa, 2022), but after a long period of use it was found to have serious teratogenic and carcinogenic adverse effects. In addition to this, it is less selective for cells and still has a killing effect on cells that are proliferating faster. In order to find a solution to the strong organ toxicity of azathioprine, researchers have conducted studies on antimetabolic immunosuppressive agents and have succeeded in extracting mycophenolate esters from Penicillium spp. fungi, which inhibit the production of antibodies and control the rejection reactions that occur during organ transplantation. In 1995, mycophenolate was approved by the US FDA as an adjunct to cyclosporine A for the prevention of acute renal transplant rejection. There are still studies in China that can show that mycophenolate, as a highly selective immunosuppressant, can replace azathioprine in combination with hormones, and that the toxic effects in the treated organ are greatly reduced. Although mycophenolate esters have shown good improvements in their toxic effects, they still have a degree of significant gastrointestinal irritation (Omair et al., 2015), which limits their widespread use. Meanwhile, researchers succeeded in synthesizing cyclosporine in 1980 and then tacrolimus in 1984, and these mTOR inhibitors showed good immunosuppressive effects and greatly reduced adverse effects such as myelosuppression. In order to maximize the pharmacological effects of cyclosporine, researchers subsequently extracted and discovered sirolimus and imidazolobine, which were combined with cyclosporine, and found that the former and the latter had increased efficacy due to synergistic effects (Kahan, 1999). In the 21st century, more attention has been given to the development of monoclonal antibodies in order to further improve the targeting and duration of drug delivery. As a result, baximab and daximab were introduced. It was found that monoclonal drugs have a longer half-life, which can improve the dosing time to some extent. Because cyclosporine is widely used, but its nephrotoxic reactions are very obvious, so in recent years, researchers have tried to modify its structure, and finally obtained a new generation of calmodulin inhibitors - a cyclosporine derivative, vircristine, developed by Isotechnika, a Canadian company. This derivative has a better immunosuppressive effect and fewer adverse effects than cyclosporine and tacrolimus, and is widely used in autoimmune diseases such as psoriasis. In March 2021, it was also approved for the treatment of systemic lupus erythematosus in the US. In addition, studies are currently underway to investigate its use in COVID-19.
However, despite our previous adequate development of immunosuppressive drugs, there is still confusion and blind spots regarding the clinical use of immunosuppressive drugs. To date, the mechanism of efficacy of immunosuppressive agents has relied on their inhibition of lymphocyte proliferation and suppression of immune system-associated cytokine production. However, it is clear that there are many signaling pathways in the body that regulate cytokine production, thus complicating the impact of immunosuppressive agents at the molecular level. For example, as a common immune-related cytokine, its gene expression is regulated by many pathways, such as PP2A-GSK3β-MCL-1, PI3K-AKT-mTOR, MAPK and so on. On top of this, there are many targets on each signaling pathway, including proteins, kinases, DNA, etc. This complexity of organismal pathways greatly calls for a more refined classification of immunosuppressive agents, which can lead to greater clarity in drug use. To date, a number of immunosuppressive agents based on targets in signaling pathways have been introduced to the market. The first immunosuppressant to enter the public eye and clinical trials targeting the JAK-STAT pathway was tofacitinib, which is now approved by the FDA for autoimmune diseases such as rheumatoid arthritis. In addition to tofacitinib, rheumatoid arthritis has been pursued for targeted therapies for the past decades, and the advent of JAK inhibitors such as Filgotinib and Upadacitinib has led to promising treatment results in randomized controlled trials for this disease (Biggioggero et al., 2019). In the treatment of rheumatoid arthritis, sulforaphane can also exert its effects by inhibiting the MAPK pathway as well as the NF-kB pathway (see the MAPK pathway section in the main text for the specific mechanism of this part). Subsequently, studies on other autoimmune diseases on the JAK-STAT pathway and the development of targets have gradually increased, and a large amount of experimental data as well as clinical evidence support the possibility of developing immunosuppressive agents on this pathway, and clinical trials for some other indications, such as graft-versus-host rejection, transplantation, asthma, and lupus (Dowty et al., 2014; Okiyama et al., 2014; Furumoto et al., 2017), have been successfully conducted and obtained satisfactory results. While the JAK-STAT pathway has been methodically studied, many discoveries have been made in other pathways, for example, sirolimus, which acts in the PI3K-AKT-mTOR pathway, has long been approved as an immunosuppressant for the prevention of immune rejection of organ transplantation; berberine and curcumin, which act in the Keap1/ARE-Nrf2 pathway, have also demonstrated their anti-inflammatory efficacy, providing a basis for future The development of immunosuppressive agents has laid the foundation for future development. At present, there are already a variety of drugs that act on the target in the clinic, and the drugs that can act on the same target show similar physicochemical properties and conformational relationships, which to a certain extent has facilitated the development of new drugs and the transformation of old drugs. This new focus on further clarification of the pharmacological mechanisms as well as the targets of action of immunosuppressive drugs can be attributed in part to the prevalent disease complexity and the growing need for precision therapy and combination drug use. This article focuses on reviewing the latest research advances in immunosuppressive drugs, which will facilitate the clinical use of immunosuppressive drugs and improve the status of combinations. In addition, this review will introduce the common immune-related signaling pathways in the body, including JAK-STAT, NF-kB, PI3K-AKT-mTOR, MAPK, Keap1-Nrf2-ARE, and for each specific pathway, summarize the targets that immunosuppressive drugs can act on, and list the representative drugs that have been marketed in the clinic and in clinical trials.

**JAK-STAT Pathway**

The JAK-STAT pathway was discovered by Darwell when he studied the signaling molecules required for the activation of target genes after the action of interferon (Darnell, 1998), and it is one of the main mechanisms regulating the production of cytokines. More than 50 cytokines, growth factors and hormones, such as interleukins, interferons, granulocytes/macrophages colony-stimulating factor, erythropoietin, and thrombopoietin, etc., by intercalating with transmembrane receptors, this brings them spatially close to JAK kinase, which changes the spatial conformation of JAK kinase and makes it susceptible to trans-activation. Activated JAK kinases promote STAT monomer phosphorylation and further dimerization, nuclear translocation, and binding to specific enhancer sequences of target genes in dimeric or more complex oligomeric forms, thus functioning as classical transcription factors. For example, STAT is involved in three types of transcription in immune cells, namely 1) general transcription, such as acetyltransferase, methyltransferase, p300, RNA polymerase, etc.; 2) transcription of some basic inflammation-related substances, such as IRF, NF-kB family transcription factors, etc.; 3) major transcription factors that are critical to follow the specification (Harrison, 2012; Villarino et al., 2015). The main three negative regulators involved in the negative regulation of JAK-STAT are: cytokine signaling inhibitory protein, activated STATs protein inhibitor, and protein tyrosine phosphatase. Among them, cytokine signaling inhibitory proteins negatively regulate JAK-STAT through three main mechanisms, including 1) binding to phosphorylated tyrosine on the receptor, which physically blocks the binding of STATs to the receptor; 2) binding to JAKs or the receptor, which blocks the activity of JAKs; 3) interaction of the SOCS box with the elonginB/C complex, which results in the degradation of JAKs and STATs, etc., are degraded via the ubiquitination pathway (Trentgove and Ward, 2013). Activated STATs protein inhibitors achieve inhibition of STATs through two pathways: 1) binding to dimerized STATs and masking the DNA-binding region of STATs; and 2) binding to STATs monomers thereby hindering their dimerization. Protein tyrosine phosphatases block the activity of JAKs by dephosphorylating them through binding to JAKs.
and receptors, in addition to negatively regulating STATs (Quintás-Cardama and Verstovsek, 2013). CBP/p300 is a histone acetyltransferase that regulates the acetylation of STATs (Wieczorek et al., 2012), which would affect the signaling of NF-κB pathway, transcriptional activity and stability of STATs homodimers, and apoptosis (Ginter et al., 2013; Zhuang, 2013) (Figure 1). It was found that IL-6, IL-13, IL-22, granulocyte colony-stimulating factor and IFN exert their biological functions mainly by binding to JAK1, while IL-2, IL-4, IL-17, IL-15 and IL-21 exert their biological functions mainly by binding to JAK3 (O’shea et al., 2002). The pathways generally work together to regulate the cell through interactions such as mutual synergy, with large and small connections arising between each pathway. For example, because both STAT2 and PI3K proteins have SH2 structural domains on them, both can bind to these phosphorylated receptors and function when JAK proteins are activated and tyrosine residues on the receptors are phosphorylated. That is, the STAT2 protein on the JAK-STAT pathway and the PI3K protein on the PI3K-AKT-mTOR pathway have a synergistic effect, and they can jointly regulate signaling between cells (Ma et al., 2010). In addition, the JAK-STAT pathway can also interact with the MAPK/ERK pathway. A protein called Grb2, which plays an important role in the MAPK/ERK pathway, also has an SH2 structural domain and

**FIGURE 1** | Mechanistic map of the JAK-STAT signaling pathway. CBP, calmodulin-binding peptide; GF, growth factor; IRF9, interferon regulatory factor 9; PIAS, protein inhibitor of activated STAT; SHP1, Src homology region 2 domain-containing phosphatase 1; SOCS, suppressor of cytokine signaling; TC-PTP, T-cell protein tyrosine phosphatase. The figure is created with BioRender.com.
can also act on the phosphorylated receptor, thus acting synergistically with the two outer pathways (Xu and Qu, 2008). JAK-STAT can also indirectly activate the MAPK pathway through SOCS3, which can bind RasGAP, a negative regulator of the MAPK pathway, and thus exert a role in promoting the MAPK pathway (Herranz et al., 2012). Numerous studies have demonstrated that the activation of STATs is mostly accomplished not by JAKs but by receptor tyrosine kinases, by two mechanisms. One is that activation of some RTKs, including epidermal growth factor receptor and platelet-derived growth factor receptor, leads to the completion of STATs tyrosine phosphorylation via Src kinase. The other is that activation of the RTK/Ras pathway causes upregulation of mitogen-activated protein kinase activation, with MAPK specifically phosphorylating a serine (Ser) at the C-terminus of most STATs, and Ser phosphorylation greatly enhances the transcriptional activity of STATs (Coskun et al., 2013). Because of its involvement in the pathogenesis of many diseases, such as solid tumors, leukemia, lymphoma, and inflammatory diseases, a large number of studies on targeted therapies for this pathway have proliferated, with JAKs and STATs as the most common targets. For example, the STAT inhibitor Fludarabine has been approved for the treatment of B-cell chronic lymphocytic leukemia; the JAK inhibitor Upadacitinib has been approved for the treatment of moderately to severely active rheumatoid arthritis or active psoriatic arthritis; and the STAT inhibitor Stattic can exert an inhibitory effect on the auto-inflammatory response in myeloid, lymphatic and neuronal tissue compartments by inhibiting STAT3 (Alhazzani et al., 2021). In addition, this pathway can be inhibited by inhibiting the binding of STAT to DNA. For example, Rabies virus P protein can downregulate type I IFN production by inhibiting STAT1 binding to the DNA structural domain (Vidy et al., 2007); Phosphotyrosyl Peptides PY*LKT, PY*L, AY*L (where Y* represents phosphotyrosine) can block this pathway by inhibiting STAT1 or STAT3 binding to DNA (You et al., 2020). CBP and p300 are essential transcriptional co-activators and histone acetyltransferases in cells, and overexpression or mutation of these two may cause the development of related diseases such as cancer, so inhibitors targeting them can also block the JAK-STAT pathway and thus play a therapeutic role. For example, Y08197 is a new inhibitor of this target with an indication of activity for the treatment of prostate cancer (Zou et al., 2019). Some of the JAK inhibitors and STAT inhibitors have been approved for marketing, while most of the drugs are still in the process of clinical trials or even animal studies, as shown in Table 1, which lists some of the drugs targeting the JAK-STAT pathway and their targets, indications, and stages of study.

Tofacitinib, developed by Pfizer, selectively inhibits JAK1 kinase, JAK2 kinase, and JAK3 kinase, and in a study of its stereocchemical structure, Meyer et al. found that the chiral structure of tofacitinib determines its binding to the JAK receptor (Meyer et al., 2010). In their study, O’shea et al. found that the drug inhibited JAK1 kinase and JAK3 kinase to a greater extent than JAK2 kinase (O’Shea et al., 2015). In addition to this, the researchers found that tofacitinib had negligible activity against TYK2 (Zerbini and Lomonte, 2012). In 2020, the FDA approved it for the treatment of chronic idiopathic arthritis (including rheumatoid arthritis, psoriatic arthritis, ankylosing spondylitis, and juvenile idiopathic arthritis) through a risk assessment and mitigation strategy. In addition to rheumatoid arthritis and ulcerative colitis, tofacitinib can also be used to prevent immune reactions to organ transplants, as well as baldness and psoriasis, for which the application is still in clinical trials. After oral administration of tofacitinib, its absolute bioavailability is 74%, peak blood concentration is reached 1–2 h after dosing, and half-life is about 3 h. A high-fat diet does not affect AUC, but it decreases Cmax by 32%. When tofacitinib was administered intravenously, Vd = 87L and the drug was distributed to an equal extent in red blood cells and plasma. The metabolism of tofacitinib is mainly metabolized by the hepatic drug enzymes CYP3A4 and CYP2C19, and 30% is excreted by the kidneys in the form of the prototype drug. Kostovic et al. found that the pharmacological activity of the metabolites of tofacitinib was less than 10% of that of the prototype drug, proving that the pharmacologically active form of the drug is the prototype drug (Kostovic et al., 2017).

JAK inhibitors have been shown to increase the risk of herpes virus infection in the treatment of ulcerative colitis and psoriasis, demonstrating that JAK inhibitors have the ability to The side effect of reducing the immunity of the body and thus inducing infection. In addition, while tofacitinib has shown good efficacy, studies have statistically found that it also shows a risk of venous embolism. Although no thorough studies have shown that JAK inhibitors are harmful to pregnant or lactating women, long-term statistical observations have shown that they are teratogenic and should be avoided in pregnant and lactating women. In addition, the use of JAK inhibitors can also promote the course of hyperlipidemia, malignancy, and gastrointestinal perforation, thus suggesting the need for more caution in drug use (Agrawal et al., 2020). In addition to JAK inhibitors, STAT inhibitors can also exhibit side effects similar to those of JAK inhibitors, and Wong et al. found that two patients developed unusual infections with symptoms of herpes virus infection as well as acute epididymitis during a clinical trial of the novel STAT3 inhibitor OPB-51602, warning of the safety of its use (Wong et al., 2015).

**NF-κB Pathway**

NF-κB pathway is an important potential target pathway for drug treatment of diseases in human body. Since nuclear factor-κB is a common class of pro-inflammatory factors, this pathway is closely related to invasive response, inflammatory response, angiogenic and metastatic response. With the gradual research, it reflects the association between NF-κB pathway and many cancer and inflammatory diseases, such as viral infection, AIDS, arthritis, atherosclerosis, asthma, diarrhea, etc. (Gupta et al., 2010b). In mammals, NF-κB can be divided into five species, namely RelA (p65), RelB, c-Rel, NF-κB1 (p50) and NF-κB2 (p52). These five parts ensure their interconnection through the conserved Rel homology structural domains and even further form heterodimers or homodimers (Prescott and Cook, 2018). In
### Table 1 | Targets in and inhibitors targeting the JAK-STAT pathway.

| Target | Agent | Phase | Indication | References |
|--------|-------|-------|------------|------------|
| JAK1   | Filgotinib | approved | Rheumatoid Arthritis, Ulcerative Colitis | Dhillon and Keam (2020); Labetoulle et al. (2018) |
|        | Upadacitinib | approved | Psoriatic Arthritis, Rheumatoid Arthritis, Atopic Dermatitis | Ferreira et al. (2020); Avci et al. (2021); Ross and Magrey, (2021) |
|        | Abrocitinib | investigational | Atopic Dermatitis | Ferreira et al. (2020) |
|        | Itacitinib | investigational | Graft versus Host Disease | Schroeder et al. (2020) |
|        | Solcitinib | investigational | Severe ulcerative Colitis | De Vries et al. (2017) |
| JAK2   | Fedratinib | approved | Myeloid proliferative tumor, Myelofibrosis | Talpaz and Kladjian, (2021) |
|        | AZD1480 | investigational | Solid Malignancies, Post-Polycthema Vera Myelofibrosis, Primary Myelofibrosis | Hedvat et al. (2009) |
|        | BMS-911543 | investigational | Myeloproliferative Disorders | Purandare et al. (2012) |
|        | Gandonitinib | investigational | Myeloproliferative Neoplasms | Berdeja et al. (2018) |
|        | Pacritinib | investigational | Acute Myeloid Leukemia | Komrokji et al. (2011) |
|        | XL-019 | investigational | Polychthema Vera, Myelofibrosis | Tam and Verstovsek, (2013) |
|        | AG490 | experimental | Subarachnoid Hemorrhage, Prostate Cancer | An et al. (2018) |
| JAK3   | Ritidecitinib | investigational | Rheumatoid Arthritis, Altopia Areata | Montilla et al. (2019); Robinson et al. (2020) |
| TYK2   | Deucravacitinib | investigational | Psoriasis | Catlett et al. (2021) |
|        | Ropsacitinib | investigational | Severe Plaque Psoriasis | Nogueira et al. (2020) |
|        | Baricitinib | approved | Atopic Dermatitis | Wallace et al. (2018) |
|        | Ruxolitinib | approved | Myeloid proliferative tumor, Graft versus Host Disease | Chen et al. (2021) |
|        | Momelotinib | investigational | Myelofibrosis, Post-Polycthema Vera Myelofibrosis | Tyner et al. (2010) |
|        | Baricitinib | approved | Myeloid proliferative tumor, Graft versus Host Disease | Wallace et al. (2018) |
|        | Decernotinib | investigational | Rheumatoid Arthritis | Mahajan et al. (2015) |
|        | Brequitinib | investigational | Severe ulcerative colitis, Cicatricial Alopecia | Montilla et al. (2019); D’Amico et al. (2018) |
|        | Nitroxazide | experimental | Myeloid proliferative tumor | Nelson et al. (2008) |
|        | Ociclopinib | approved | Dermatitis (dogs) | Rynhoud et al. (2021) |
|        | Tolacitinib | approved | Rheumatoid Arthritis, Psoriatic Arthritis, Juvenile Idiopathic Arthritis, Ulcerative Colitis | Kurasawa et al. (2018) |
|        | Lenstarinib | investigational | Acute Myeloid Leukemia | Knapper et al. (2017) |
|        | Cerdulatinib | investigational | Lymphoid Leukemia, B-Cell Chronic Lymphocytic Leukemia | Coffey et al. (2019) |
|        | Delgocitinib | investigational | Atopic Dermatitis | Dhillon, (2020) |
|        | Gusacitinib | investigational | Atopic Dermatitis | Le et al. (2021) |
|        | Palitinib | investigational | Rheumatoid Arthritis | Qiu et al. (2019a) |
| STAT1  | Fludarabine | approved | Burkitt Lymphoma, Mantle Cell Lymphoma, Marginal Zone Non-Hodgkin Lymphoma | Izutsu et al. (2021) |
|        | Static | approved | Ankylosing Spondylitis | Schust et al. (2006) |
|        | BP-1-102 | investigational | Carcinogenesis, Neoplasm | Uchihara et al. (2019) |
|        | PLLLLLL32 | investigational | Neoplasm | Onimoe et al. (2012) |
|        | LLL-12 | investigational | Inflammatory Disease, Acute Lung Injury | Lin et al. (2010a) |
|        | Ochrornycinone | investigational | Psoriasis | Boonlarpradab et al. (2013) |
|        | OPB-3112 | investigational | Leukemia | Leung et al. (2015a) |
|        | OPB-51602 | investigational | Nasopharyngeal Carcinoma, Advanced Cancer, Multiple Myelomas, Non-Hodgkin Lymphoma, Acute Myeloid Leukemia, Chronic Myeloid Leukemia, Malignant Solid Tumor | Leung et al. (2015a) |
|        | Pyrimethamine | investigational | Chronic Lymphocytic Leukemia, Small Lymphocytic Leukemia, Malaria | Takakura et al. (2011) |
|        | Resveratrol | investigational | Herpes labialis infections | Meng et al. (2021) |
|        | STX-0119 | investigational | Glialblastoma, Neoplasm | Siddiquee et al. (2007) |
|        | Cryptotanshinone | experimental | Burkitt Lymphoma | Wu et al. (2020a) |
|        | Ocurbitasina | experimental | Neoplasm | Guo et al. (2018) |
|        | Ocuproline | investigational | Motor and phonic tics | Nelson et al. (2011) |
| STAT5  | Pimozide | approved | Neoplasm, Polyplody | Leung et al. (2015b) |
|        | Cpd1 | investigational | Acute Myeloid Leukemia | Page et al. (2012) |

(Continued on following page)
the unactivated state, the NF-κB dimer binds tightly to the kappa B protein inhibitor in order to maintain the stability of the NF-κB dimer and inhibit its entry into the nucleus to interact with DNA. Activation of the NF-κB pathway can be divided into typical and atypical pathways, with the former involving IKK (a heterodimer composed of IKKα, IKKβ, IKKγ, and NEMO, of which IKKβ is the catalytic subunit), IkB, and NF-κB (e.g., p65/p50 heterodimer), including the TNF-α pathway, the IL-1β pathway, and the cellular stress pathway (Lin et al., 2010b). Among the classical pathways, the TNF-α pathway is the most well studied, and its activation pathway is as follows: after TNF-α and TNFFR binding, IKK is aggregated in TNFR1 with the help of TRAF2/5 and receptor-interacting protein kinase, and then, receptor-interacting protein kinase mediates IKK phosphorylation to activate it, in which MEKK3 or TAK1 is involved in the phosphorylation process (Devin et al., 2000). The catalytic subunit IKKβ is re-activated and then activates serine residues 32 and 36 of IkB, and further polyubiquitination and degradation of IkB by the proteasome. After this process, the NLS of p100 is exposed, promoting the p65/p50 nuclear translocation. Subsequently, p65/p50 binds to DNA and undergoes transcription, which is regulated by phosphorylation and acetylation of the p65 subunit, resulting in Bcl, p100, IL-8, IL-1β, TNF-α, A20, COX2, MIP-2, etc (Yang et al., 2001b) (Figure 2). The non-classical pathway includes CD40 pathway, LTβ pathway, etc. Unlike the classical pathway, the non-classical pathway mainly relies on NF-κB-inducible kinase (NIK) to activate IKKα, which in turn triggers the cleavage of p100 to p52. P52 in turn binds to RelB in a complex and undergoes nuclear translocation, binding to DNA and thus enhancing gene expression (Chen, 2005). In addition, through the cIAP protein, the classical and non-classical pathways can in turn be regulated by each other (Zarnegar et al., 2008). The current common targets and corresponding drugs are listed in Table 2.

Artemisinin is now publicly recognized as an effective drug for the treatment of malaria and has helped many countries around the world that are afflicted by the malaria disease. Mechanistically, artemisinin inhibits TNF-induced phosphorylation of NF-κB reporter factor IκBα and its degradation by the proteasome, nuclear translocation of p65, and kinases upstream of IKK thereby achieving inhibition of the NF-κB pathway, thereby regulating genes related to cell proliferation, survival, invasion, and angiogenesis, such as Bcl, COX-2, MMP9, VEGF (Awasthee et al., 2019). As early as 2017, Wang et al. should have speculated on the possibility of artemisinin for the treatment of inflammation and cancer (Wang et al., 2017), and corresponding clinical trials are actively underway. In September 2021, clinical trials on the safety and efficacy of the herbal agent artemisinin for use in COVID-19 subjects were conducted, further demonstrating that its research on inflammation due to viral infections is still being explored.

### Table 1: Targets in and inhibitors targeting the JAK-STAT pathway.

| Target | Agent | Phase | Indication | References |
|--------|-------|-------|------------|------------|
| STAT3/STAT5 | SH-4-54 | experimental | Classic Hodgkin Lymphoma, Neoplasm | Cui et al. (2020) |
| STAT3/STAT6 | Panobinostat | approved | Multiple Myeloma | Breuer et al. (2020) |
| STAT3/TAX | Niclosamide | approved | Hymenolepiasis, Diphylllobothriasis | Kadi et al. (2018) |
| STAT3/IL-2 | CMD178 | experimental | B-cell non-Hodgkin Lymphoma | Price-Troska et al. (2019) |
| Apoptosis inducing Factor/STAT3 | Alprimod | investigational | Multiple Lymphoma | Coker-Gurkan et al. (2021) |

The table above lists some of the inhibitors targeting the JAK-STAT pathway, along with their respective targets, phases, and indications. The table provides a comprehensive overview of the current state of research in the field.
The most common target in the NF-κB pathway is IKKβ, but IKKβ inhibitors are still less widely used in the clinic and are currently being developed at a lower rate, which has more to do with their safety profile. In fact, the NF-κB pathway is often considered as a “double-edged sword”, its anti-inflammatory response varies with the condition, for example, immune cells in tumors can play a dual role under the regulation of the pathway, which can be anti-inflammatory and anti-tumor response, but also can promote the development of tumor immune escape response (Ben-Neriah and Karin, 2011; Taniguchi and Karin, 2018). In addition, IKKβ inhibitors in the NF-κB pathway have more pronounced host differences, which may result from species variation or human host dependence (Prescott and Cook, 2018), which also makes it difficult to analyze the correlation between preclinical studies and clinical trials, and the difficulty of further drug development.
### TABLE 2 | Targets in and inhibitors targeting the NF-κB pathway.

| Target | Agent           | Phase               | Indication                                                                                           | References                                                                                   |
|--------|-----------------|---------------------|------------------------------------------------------------------------------------------------------|------------------------------------------------------------------------------------------------|
|        | IKK inhibitor    |                    |                                                                                                      |                                                                                                |
|        | IKKβ            | approved            | Infection, Diarrheal                                                                                  | Pierpaoli et al. (2021); Yao et al. (2015); Pandey et al. (2008)                                |
|        | Berberine       | approved            | Pediatric Ulcerative Colitis, Neurodegenerative Disease, Vascular Dysfunction                        | Prisco et al. (2020); Lo Cascio et al. (2021)                                                  |
|        | Curcumin        | approved            | Hypoxic Respiratory Failure                                                                           | Reynaert et al. (2004); Manrique-Gil et al. (2021)                                         |
|        | Nitric oxide    | approved            |                                                                                                      | Kapahi et al. (2000); Ivanov and Hei, (2013)                                                     |
|        | Arsénite        | investigational     | Neoplasms                                                                                           | Das et al. (2021); Logie and Vanden Berghe, (2020)                                          |
|        | Withaferin A    | investigational     | Cognitive Dysfunction, Inflammation                                                                | Sandra et al. (2005); Sandra et al. (2006); Victoriano et al. (2006)                          |
|        | ACHP            | experimental        | Multiple Myeloma, Adult T-cell Leukemia, HIV-1 Replication                                           | Frelin et al. (2005)                                                                        |
|        | AS602868 Bay 65–1942 | experimental | KRAS-induced Lung Cancer, Chronic Pulmonary Inflammation, Ischemia-reperfusion Injury, LPS-induced Neurotoxicity | Bassières et al. (2014); Ziegelbauer et al. (2005); Moss et al. (2007); Zhang et al. (2010) |
|        | BI 605906       | experimental        | Inflammation                                                                                       | Ba et al. (2019)                                                                              |
|        | Butein          | experimental        | Neoplasms                                                                                            | Tuli et al. (2021); Pandey et al. (2007)                                                      |
|        | EqM             | experimental        | Leukemia, Colon, Kidney Cancer                                                                      | Li et al. (2010)                                                                             |
|        | IKK-16          | experimental        | Multiple Organ Failure Associated with Hemorrhagic Shock, Sepsis-associated Multiple Organ Dysfunction, Ventilation-induced Lung Injury, Acute Kidney Injury | Kanduri et al. (2011); Ochiai et al. (2008); Uota et al. (2012); Tanaka et al. (2006)           |
|        | IMD-0354        | experimental        | Chronic Lymphocytic Leukemia, Pancreatic Cancer, Adult T-cell Leukemia, Breast Cancer                | Deng et al. (2015)                                                                            |
|        | LY2409881       | experimental        | Diffuse Large B-cell Lymphoma                                                                        | Hideshima et al. (2006); Schopf et al. (2006)                                                  |
|        | MLN120B         | experimental        | Multiple myeloma, Arthritis                                                                          | Sommers et al. (2009a); Sommers et al. (2009b)                                               |
|        | PF 184          | experimental        | Arthritis                                                                                           | Moláievé et al. (2009); Sommers et al. (2009c); Rajendrasozhan et al. (2010)                   |
|        | PHA-408         | experimental        | Arthritis, Chronic Obstructive Pulmonary Disease                                                     | Frew and Krek, (2008); Wang et al. (2016)                                                       |
|        | pVHL            | experimental        | Neoplasms                                                                                            | Kishore et al. (2003); Johnson et al. (2014); Liu et al. (2013); Negi and Sharma, (2015)        |
|        | SC-514          | experimental        | Rat Model of Inflammation, Oral Squamous Cell Carcinoma, Osteoclast-related Disorders, Diabetic Neuropathy | Podolin et al. (2005); Sachse et al. (2011); Du et al. (2012); Nan et al. (2014); Birrell et al. (2006); Lu et al. (2014) |
|        | TPCA-1          | experimental        | Arthritis, Nasal Epithelium Inflammation, Glioma, Non-small Cell Lung Cancer, Chronic Obstructive Pulmonary Disease, Wet-type Age-Related Macular Degeneration | Dong et al. (2015); Du et al. (2012); McIntyre et al. (2003); MacMaster et al. (2003); Townsend et al. (2004); Buontempo et al. (2012); Ping et al. (2016) |
|        | IKKα, IKKβ      | experimental        | Inflammation                                                                                       | Francis et al. (2020); Olsen et al. (2004)                                                     |
|        | Ainsladimer A   | experimental        | Arthritis, Colitis, Cardiac Graft Rejection, Acute T-lymphocytic Leukemia, Glioma, Prostate Cancer | Bernier et al. (2006); Macejová et al. (2020)                                                  |
|        | BMS-345541      | experimental        | Pericardial Diseases                                                                                 | Hideshima et al. (2002); Lam et al. (2005); Vodanovic-Jankovic et al. (2006); Choi et al. (2016) |
|        | BOT-64          | investigational     | Solid Tumor                                                                                         | Nagini et al. (2021); Gupta et al. (2010a)                                                    |
|        | CHS828          | experimental        | Neoplasms                                                                                            | Hideshima et al. (2002); Lam et al. (2005); Vodanovic-Jankovic et al. (2006); Choi et al. (2016) |
|        | Manumycin A     | experimental        | Neoplasms                                                                                            |                                                                                               |
|        | Nimboide        | experimental        | Multiple Myeloma, Diffuse Large B-cell Lymphoma, Graft-versus-host Disease, Tobacco Smoke-induced Pulmonary Inflammation |                                                                                               |
|        | PS-1145         | experimental        |                                                                                                      |                                                                                               |
More surprisingly, it was found that inhibition of IKKβ in certain cells or tissues exacerbates inflammation spontaneously, making drug use less safe and certain. Charles et al. found that IKKβ inhibited tumor growth in Colla2-expressing fibroblasts in a CAC model, but this was strictly dependent on increased secretion of HGF, and their speculation is that IKK may have different functions in different subpopulations of cells or tissues exacerbates in

PI3K-AKT-mTOR Pathway

PI3K/AKT/mTOR pathway is one of the most important signaling pathways in human body, which plays a crucial role in the activation of various downstream effector molecules and is involved in the regulation of cell proliferation, differentiation, apoptosis, autophagy, invasion and metastasis, etc. In response to stimulating factors such as growth factors and cytokines, residues on the transmembrane phosphorylated tyrosine kinase interact with the SH2 structural domain on PI3K, relieving the inhibitory effect of p58 on p110, i.e., the dimeric conformation is altered, leading to activation of PI3K (Osaki et al., 2004). In addition, PI3K activation can be accomplished by direct recognition and binding of Ras to p110. PI3K activation leads to the conversion of 3,4-bisphosphatidylinositol (PIP2) to 3,4,5-trisphosphatidylinositol (PIP3). The generated PIP3 recognizes each other with the PH structural domain of AKT, which results in the transfer of AKT from the cytoplasm to the cytosol, along with a conformational change of AKT, exposing threonine proteins as well as serine proteins. AKT is activated by the co-activation of Thr308 phosphorylation in the presence of PDK1 and Ser743 phosphorylation in the presence of PDK2 (Ma and Blenis, 2009). AKT is activated and translocated to the cytoplasm or nucleus, where it targets and regulates downstream signaling

| Target | Agent | Phase | Indication | References |
|--------|-------|-------|------------|------------|
| IKK complex | 5-fluorouracil | approved | Salivary Gland Cancer | Azuma et al. (2001) |
| | NBD peptide | experimental | Osteoclastogenesis, Inflammation | Jmi et al. (2004); May et al. (2000) |
| | vfl-10 | experimental | Nasopharyngeal Carcinoma | Ren et al. (2016) |
| | GSK 319347A | experimental | Reperfusion Injury | Zeng et al. (2019) |
| Multiple targets | IKKa, IκBa | investigational | Cutaneous Metastatic Melanoma | Shankar et al. (2017); Gheorgheosu et al. (2014) |
| | IKKβ, IκBa | Aspirin | approved | Pain, Fever, Inflammation | Alfonsio et al. (2014); Kopp and Ghosh, (1994); Yin et al. (1998) |
| | | Exisulind | investigational | Non-Small-Cell Lung Carcinoma, Prostate Cancer | Bunn et al. (2002); Webster and Leibovich, (2005) |
| | | Sulindac sulphide | experimental | Neoplasm | Yamamoto et al. (1999); Ekanem et al. (2020) |
| | IκBa, p65 | Artemisinin | investigational | Schizophrenia, COVID-19 | Uckun et al. (2021); Saeed et al. (2016); Wang et al. (2017) |
| | IKKβ, NF-κB | Arsenic trioxide | approved | Acute Promyelocytic Leukemia | Mathas et al. (2003); Yousefshia, (2021) |
| | TANK-binding,IKKε | Doxycycline | approved | Infections | Ogut et al. (2016) |
| | p68 | Amleroxan | approved | Non-Small-Cell Lung Cancer, Aphthous Ulcers | Reilly et al. (2013); Challa et al. (2016) |
| | | | | | |
| p65 acetylation inhibitor | p65 | Gallic acid | approved | Diarrhea | Choi et al. (2009); Sung et al. (2008); Hemshekhar et al. (2012) |
| | | Anacardic acid | experimental | Neoplasm | Yang et al. (2001a); Sreenivasan et al. (2003) |
| protein phosphatases inhibitor | | Cytosine arabinoside | approved | Acute Leukemia | Chew et al. (2009); Yu et al. (2011a); Sreenivasan et al. (2003) |
| | IκBa | WIP1 | experimental | No Data | Sunwoo et al. (2001); Lun et al. (2005); Khalesi et al. (2021) |
| | | | | | Snirvastava et al. (2016); Singh and Aggarwal, (1995) |
| | | Bortezomib | approved | Multiple Myeloma, Mantle Cell Lymphoma | Nguyen et al. (2014); Li et al. (2014) |
| | | Phenyllarsine oxide | experimental | Edema | Guo and Peng, (2013) |
| | NF-κB | MG115 | experimental | No Data | Watanabe et al. (1986) |
| | | MG132 | experimental | Neoplasm | Watanabe et al. (1986) |
| | | TLCK | experimental | Inflammation | Lin et al. (2018); Umezawa, (2006) |
| | NF-κB, RelA | TPCK | experimental | Neoplasm | |
| | | NBD peptide | experimental | Osteoclastogenesis, Inflammation | Jimi et al. (2004); May et al. (2000) |
molecules, including mTOR. The nodular sclerosis complex-1 (TSC-1) and nodular sclerosis complex-2 (TSC-2) can form a dimeric complex that further inhibits the GTPase Rheb, which is required to stimulate mTOR activation, so the TSC-1/TSC-2 complex has an inhibitory effect on mTOR activation. However, the activation of AKT can release the inhibition of mTOR by TSC-1/TSC-2, thus allowing the smooth activation of mTOR. In addition, AKT can also act directly on mTOR1 to activate mTOR (Huang and Manning, 2008). Phosphorylated mTOR further regulates ribosomal S6 protein kinase (S6K) and the eukaryotic initiation factor 4E-binding protein 1 (4E-BP1), which promotes phosphorylation of ribosomal S6 proteins and inactivates 4E-BP1 by phosphorylation. This leads to the synthesis of ribosomal proteins and the initiation of protein translation processes, respectively (Wan and Helman, 2007) (Figure 3). Since this pathway is shown to be dysregulated in various tumors and inflammatory diseases, this shows great promise for the study of this pathway. Researchers have identified and developed a number of drugs that target this pathway, which can be broadly classified as PI3K inhibitors, AKT inhibitors, mTOR inhibitors, and dual PI3K/mTOR inhibitors. These inhibitors inhibit the activation of PI3K, AKT, and mTOR by inhibiting these three targets, which in turn is closely linked to the degree of tumor metastasis and related disease progression. A large number of preclinical studies and clinical trials on these inhibitors exist today to ensure safety and efficacy during drug use. Table 3 provides a summary of some of the inhibitors for different targets, with information about their indications.

The PI3K/AKT/mTOR pathway is associated with many diseases, and there are many factors that affect the physiological status of the human body in addition to the three critical targets of PI3K, AKT, and mTOR. For example, PTEN, a tumor suppressor, blocks the activation of PI3K/AKT/mTOR pathway by inhibiting the transition from PIP2 to PIP3. It was found that PTEN knockout mice had abnormally high levels of PIP3 compared to normal mice, and AKT remained continuously activated, which in turn induced tumorigenesis (Papa et al., 2014; Haddadi et al., 2018). In addition, the knockout mice also showed hypoglycemia, suggesting that it also has some effect on blood glucose regulation in vivo (Nguyen et al., 2006).

Sirolimus is a first-generation mTOR inhibitor targeting mTORC1, which specifically acts on mTORC1, causing phosphorylation of the carboxy terminus of mTOR and loss of catalytic activity, blocking the immune response triggered by interleukin-2, interleukin-15 and CD28/B7 co-stimulatory pathway to activate mTOR. It can inhibit the growth and proliferation of immune cells by keeping them in the G1/S phase, in addition to inhibiting the synthesis of immune molecules such as interleukin-1. Nowadays, it is mainly used in clinical practice to prevent rejection after organ transplantation and to treat autoimmune diseases (Weichhart, 2018; Li et al., 2019). Nowadays, indications for sirolimus are gradually being developed. For example, in primary immune thrombocytopenia, decreased Treg cell levels are the main cause of refractory/recurrent ITP, which provides a theoretical basis for sirolimus treatment of ITP. After a randomized group trial by Li (Cuker and Neunert, 2016) et al. showed that sirolimus significantly improved remission rates as well as platelet counts in patients with ITP (Li et al., 2013). Jasinski et al. included 12 patients with ITP and switched to sirolimus combined with hormone therapy after conventional treatment failed and found that the patients’ cure rate was greatly improved and no significant adverse effects were observed during the use of the drug (Jasinski et al., 2017), further establishing the possibility of sirolimus for the treatment of immune thrombocytopenia. Blood levels peaked after 1 h in healthy subjects after administration of sirolimus. In stable renal transplant patients, the half-life of sirolimus can be monitored to be approximately 46–78 h. The study demonstrated that the mean bioavailability of sirolimus tablets was 27% higher compared to the solution and that the plasma protein binding of sirolimus was 92%, with approximately 97% being bound to serum proteins. The metabolism of sirolimus is mainly carried out by CYP3A4 enzyme, and after hepatic metabolism, it is excreted out of the body mainly in the feces, and only a small amount is excreted out of the urine. Regarding the safety of sirolimus, the most common side effect was found to be grade 1–2 mucositis, in addition to many other adverse reactions such as stomatitis, oral ulcers, hyperlipidemia, infection and hepatic impairment, but it was found that most of these adverse reactions are dose dependent and the symptoms of these adverse reactions can be alleviated when the blood concentration of sirolimus decreases (Bride et al., 2016; Long et al., 2018; Chen et al., 2020b; Feng et al., 2020). In addition to mTOR inhibitors, other targets on the PI3K-AKT-mTOR pathway still exist, such as PI3K. Alpelisib was the first PI3Ka inhibitor identified and is currently approved and widely used for the treatment of breast cancer, in addition to being approved by the FDA in 2020 as a fast track for the treatment of the PIK3CA-associated overgrowth disease spectrum. During preclinical modeling, it was found to inhibit two common mutation sites of PI3K (H1047R and E545K) (Fritsch et al., 2014), in addition to having a dual mechanism of action, i.e., simultaneous inhibition of PI3K as well as induction of p110α degradation (Chang et al., 2021), and these highlight the possibility of its development as an immunosuppressive agent.

**Keap1-Nrf2-ARE Pathway**

The Keap1-Nrf2-ARE pathway is a key pathway for cellular resistance to oxidative stress and has neutralizing, antioxidant as well as detoxifying effects because it regulates antioxidant enzymes and phase II detoxifying enzymes. This pathway is often used as a drug target to treat a variety of diseases, including neurodegenerative diseases, cancer, cardiovascular diseases, respiratory diseases, and various inflammatory conditions. For example, quercetin can enhance brain function in learning memory by upregulating the expression of Nrf2 and the antioxidant gene OH-1 thereby reducing oxidative stress in the brain (Silva et al., 2017), and resveratrol can effectively protect against oxidative damage due to renal hyperglycemia mediated by upregulating antioxidant genes including catalase (CAT), GSH-Px, SOD and HO-1 (Muselin and Cristina, 2019). The Keap1-Nrf2-ARE pathway consists of three core components, Keap1, Nrf2, and...
ARE, which are activated to transcribe and express downstream antioxidant genes through various targets in this pathway. Under normal physiological conditions, most of Nrf2 couples to the Neh2 structural domain on Keap1 in an overall stable intracellular environment and anchors to the cytoplasm in conjunction with cytoplasmic agonist proteins. In contrast, under oxidative stress as well as stimulation by electrophile substances, the electrically sensitive cysteine structure on Keap1 protein is mutated, resulting in a conformational change of Keap1 (Wakabayashi et al., 2004). Changes in the structure of Keap1 cause dissociation between it and Nrf2, and the activated Nrf2 translocates into the nucleus and binds to Maf proteins in the nucleus to form a heterodimer, which in turn binds to the ARE and regulates transcription of downstream target genes (Magesh et al., 2012). Besides, the variation of Keap1 structure can also reduce the degradation of Nrf2 ubiquitination, i.e., it can make the Nrf2 protein more stable (Kensler et al., 2007). The increased stability of Nrf2 protein is also associated with the
### TABLE 3 | Targets in and inhibitors targeting the PI3K-AKT-mTOR pathway.

| Target | Agent | Phase | Indication | References |
|--------|-------|-------|------------|------------|
| PI3K inhibitor | PI3Kα | Alpelisib | approved | Advanced or Metastatic Breast Cancer | Chang et al. (2021) |
| | | GDC-0057 | investigational | Breast Cancer | Song et al. (2021) |
| | | Serabelisib | investigational | Metastatic Clear Cell Renal Cell Carcinoma, Breast Cancer, Neoplasm | Patel et al. (2019) |
| PI3Kβ | AZD-8166 | investigational | Breast and Prostate Tumors | Hancox et al. (2015) |
| | GSK2636771 | investigational | Cancer, Lymphoma, Solid Neoplasm, Recurrent Solid Neoplasm, Advanced Malignant Neoplasm | Mateo et al. (2017); Sarker et al. (2021) |
| PI3Kγ | Egalisib | investigational | Locally Advanced HPV+ and HPV- Head and Neck Squamous Cell Carcinoma | Qi et al. (2019b) |
| | | | | |
| PI3Kδ | Idevialisib | approved | Chronic Lymphocytic Leukemia, Relapsed Follicular B-cell non-Hodgkin Lymphoma, Relapsed Small Lymphocytic Lymphoma | Zirlik and Veelken, (2018) |
| | Copanlisib | approved | Relapsed Follicular Lymphoma | Munoz et al. (2021) |
| | | | | |
| | Buparlisib | investigational | Lymphoma, Metastases, Lung Cancer, Solid Tumors, Breast Cancer | Geuna et al. (2015); Xing et al. (2021) |
| | CH-5132799 | investigational | Solid Tumors | Cecarelli et al. (2021) |
| | Pictilisib | investigational | Solid Cancers, Breast Cancer, Advanced Solid Tumors, Metastatic Breast Cancer, non-Hodgkin Lymphoma | Geena et al. (2015); Xing et al. (2021) |
| | Sonolisib | investigational | Glioblastoma, Prostate Cancer, Advanced Solid Tumors, Advanced BRAF-mutant Cancers, Non-Small Cell Lung Cancer | Harder et al. (2019); Levy et al. (2014) |
| | ZSTK474 | investigational | Neoplasm | Muthiah and Callaghan, (2017) |
| AKT inhibitor | AKT | Afuresertib | investigational | Cancer, Neoplasms, Haematologic | Yamaji et al. (2017) |
| | | Erufosine | experimental | Neoplasms | Tzoneva et al. (2020); Hirai et al. (2010) |
| | | MK2206 | investigational | Relapsed or Refractory Diffuse Large B cell Lymphoma | Block et al. (2010) |
| | | | | |
| | | Perifosine | investigational | Solid Tumors, Multiple Myeloma, Leukemia (unspecified), Lung Cancer, Brain Cancer | Banerjee et al. (2013); Jabbarzadeh Kaboli et al. (2020) |
| | | SR13668 | investigational | Neoplasms | de Frias et al. (2009); Han et al. (2007) |
| | | Uprosertib | investigational | Breast Neoplasm | Chomer and Moorehead, (2018) |
| | | | | |
| | | AT7867 | investigational | Pancreatic Diseases, Thymoma, Neoplasms | Kimura et al. (2020); Grimshaw et al. (2010) |
| | | | | |
| | | AT13148 | investigational | Hypotension, Neoplasms | Pal et al. (2020) |
| | | | | |
| | | Capivasertib | investigational | Metastatic Breast Cancer | Zhu et al. (2021a) |
| | | GS190693 | investigational | Tumor, Cancer, Lymphoma | Levy et al. (2009) |
| | | Ipatasertib | investigational | Cancer, Neoplasms, Solid Cancers, Breast Cancer, Gastric Cancer | Shapiro et al. (2021) |
| | | CCT128930 | experimental | Osteosarcoma, Neoplasm | Sun et al. (2020) |
| | | H-8 | experimental | No Data | Nituiescu et al. (2016) |
| | | H-89 | experimental | No Data | Nituiescu et al. (2016) |
| | | NL-71–101 | experimental | No Data | Nituiescu et al. (2016) |
| mTOR inhibitor | mTORC1 | AZD8055 | investigational | Cancer, Lymphomas, Solid Tumors, Malignant Gloma, Brainstem Gloma | Chresta et al. (2013) |
| | | Ku-0063794 | investigational | Neoplasm | Garcia-Martínez et al. (2009) |
| | | OSI-027 | investigational | Solid Tumor, Lymphoma | Bhabat et al. (2011) |
| | | PP242 | investigational | Neoplasms, Leukemia | Feldman et al. (2009) |
| | | Vistusertib | investigational | Neoplasm | Huo et al. (2014); Pancholi et al. (2019) |
| | | PP30 | experimental | Pneumoperitoneum, Leydig Cell Tumor | Feldman et al. (2009) |
| | | Torin1 | experimental | Tuberous Sclerosis, Neoplasm | Thoreen et al. (2009) |
| | | Everolimus | approved | Breast Cancer | Ballou and Lin, (2008) |
| | | Sirolimus | approved | Organ Transplantation | Ballou and Lin, (2008) |
| | | Temsirolimus | approved | Renal Cell Carcinoma | Ballou and Lin, (2008) |
| | | Ridaforolimus | investigational | Solid Tumors, Sarcoma, Cancer/Tumors (unspecified), Endometrial Cancer, Prostate Cancer, Bone Metastases | Spreafico and Mackay, (2013) |
| | | Olcorolimus | experimental | Asthma | Eynott et al. (2003) |
| | | Zotarolimus | experimental | Thrombosis, Myocardial Infarction | Ballou and Lin, (2008) |
| | | WAY-600 | experimental | Neoplasm | Yu et al. (2009) |

(Continued on following page)
phosphorylation of its degron region under oxidative stress and the resulting conformational change, which prevents its recognition by E3 ubiquitinylination ligase, thereby weakening the recognition of Nrf2 by the protease and activating the intrinsic transcriptional activity of Nrf2. It has been shown that Nrf2, upon dissociation from Keap1, also synergistically promotes activation of the intrinsic transcriptional activity of Nrf2 by its two active regions, Neh4 and Neh5 coactivators, CBP proteins (Nguyen et al., 2005). The downstream target proteins regulated by Nrf2 have now been shown to fall into several categories: phase II metabolic enzymes, antioxidant proteins/enzymes, proteasomal/molecular partners, anti-inflammatory factors, and phase III metabolic enzymes (i.e., drug transporters). Among them, the main ones of wide interest are quinone oxidoreductase-1 (NQO1), heme oxygenase-1 (HO-1) and γ-glutamylcysteine synthetase (γ-GCS), which exert antioxidant effects and thus treat related diseases (Figure 4). Nrf2 and NF-κB pathway are key factors sensitive to redox homeostasis, and the interaction mechanism between the two may lead to a variety of diseases, such as pharmacogenic liver diseases. When a drug stimulates oxidative stress in cells, Nrf2 increases the expression of antioxidant enzymes and GSH, neutralizes ROS in hepatocytes, helps to reduce the degree of oxidative stress, and inhibits NF-κB expression; on the contrary, if Nrf2 expression is absent, NF-κB is more active at this time, leading to the accumulation of inflammatory factors (Ganesh Yerra et al., 2013). Therefore, the use of Nrf2 activators and Nrf2 inhibitors affects not only the operation of the Keap1/ARE-Nrf2 pathway, but also the NF-κB pathway. Currently, a large number of drugs targeting this pathway have entered clinical trials, while some of them only have pharmacological indications, Table 4 provides a summary of some of the drugs targeting the Keap1-Nrf2-ARE pathway, with a brief overview of their indications and stages of study, etc.

All-trans retinoic acid is an agonist of retinoic acid receptor alpha, which is a nuclear receptor agonist that inhibits the transcriptional activity of Nrf2 (Natalia et al., 2019). It was shown that all-trans retinoic acid could interfere with the dimerization between bZIP factors and small Maf proteins, which would severely affect the binding between Nrf2 and DNA (Nioi et al., 2003). In addition to this, all-trans retinoic acid can also bind to RARs as a ligand for RARs, further leading to the subnuclear relocalization of Nrf2 and affecting the delocalization of transcriptional intermediate factor 1 to the centromeric heterochromatin region (Cammas et al., 2002), all of which would demonstrate the inhibitory effect of all-trans retinoic acid on Nrf2. The treatment of acute promyelocytic leukemia is its most common use today and has been approved by the FDA for clinical treatment as early as a decade ago. All-trans retinoic acid exerts its therapeutic effect by inducing terminal dichotomization in leukemic cell lines as well as APL cells, and the first study in France found that patients with acute promyelocytic leukemia using all-trans retinoic acid had few reactions such as primary resistance and alopecia (Degos and Wang, 2001). In 2021, the FDA approved all-trans retinoic acid in combination with benzoyl peroxide in cream form for the treatment of acne vulgaris in patients 9 years of age and older, demonstrating its new use and enabling a wider range of applications. In addition to the topical treatment of acne vulgaris, it can also be used to treat psoriasis, congenital ichthyosis, ichthyosis vulgaris, lamellar ichthyosis, phyllodes keratoses and other skin conditions as well as to improve fine lines, hyperpigmentation, roughness and symptoms associated with photodamage. However, to ensure the safety and efficacy of the treatment, the related diseases are still in the clinical trial or recruitment stage. When treating skin diseases, only 1%–31% of the drug is absorbed by the skin, and when combined with benzoyl peroxide, the degree of absorption is again influenced by age. All-trans retinoic acid has a half-life of 0.5–2 h and is metabolized in the body mainly by the liver, with the end product being retinoic β-glucuronide. In safety studies of all-trans retinoic acid, it has been found that some patients develop leukocyte activation syndrome (Castaigne et al., 1990) and drug resistance (Frankel et al., 1992) after treatment of acute promyelocytic leukemia, and to minimize the occurrence of side effects, all-trans retinoic acid is now commonly used in combination with intensive chemotherapy or by high-dose injections of glucocorticoids to resist side effects (Degos and Wang, 2001).

Since the Keap1-Nrf2-ARE pathway is closely related to the body’s resistance to oxidative stress, its use as a therapeutic target can achieve considerable efficacy while excessive activation of the pathway makes it difficult to avoid adverse effects and side effects. Although this pathway can be used in the treatment of cancer, over-activation of this pathway can, on the contrary, greatly increase the chance of cancer induction and, in addition, may cause diseases such as atherosclerosis (Gonzalez-Donquiles et al.,

| Target | Phase | Indication | References |
|--------|-------|------------|------------|
| PI3K/mTOR | PI3K/mTOR | Neoplasm | Xu et al. (2009) |
| PI3K/mTOR | PI3K/mTOR | Neoplasm, Severe Combined Immunodeficiency | Yu et al. (2009) |
| PI3K/mTOR | PI3K/mTOR | Solid Cancers, Breast Cancer, Prostate Cancer, Renal Cell Carcinoma, Endometrial Carcinoma | Dofy et al. (2016) |
| PI3K/mTOR | PI3K/mTOR | Cancer, Solid Tumor, Renal Cancer, Breast Cancer, Cowden Syndrome | Yang et al. (2020) |
| PI3K/mTOR | PI3K/mTOR | Breast Cancer | Maira et al. (2008) |
| PI3K/mTOR | PI3K/mTOR | Breast Cancer, Solid Tumor, Malignant Glioma | Molkovskv and Siu, (2008) |
| PI3K/mTOR | PI3K/mTOR | Cancer | Heffron et al. (2010) |
Over-activation of Nrf2 can increase the survival advantage of tumors or even develop chemotherapy resistance, therefore, another idea for tumor treatment can be adopted, namely, targeted inhibition of Nrf2 and thus sensitization therapy. Besides, there are few natural compounds such as opium bitter alcohol and lignan that can be used as Nrf2 inhibitors in clinical practice. These would suggest that Nrf2 is a double-edged sword, and when conducting treatment, a reasonable individualized treatment plan should be designed and the correct dosing regimen should be chosen according to the patient’s condition and individual circumstances.

**MAPK Pathway**

MAPKs are a class of threonine or serine protein kinases that are expressed in all eukaryotic cells. Activation of MAPK shows a typical three-stage enzymatic cascade reaction, namely MAP3K-MAP2K-MAPK chain. Upon activation of the upstream protein by cytokines, cellular stress, hormones, and neurotransmitters, the chain shows a
| Target | Agent | Phase | Indication | Reference |
|--------|-------|-------|------------|-----------|
| Nrf2 inhibitor | Nrf2 | All-trans-retinoic acid | approved | Acute Promyelocytic Leukemia, Neoplasm | Giuli et al. (2020); Wang et al. (2007); Chen et al. (2002); Tarumoto et al. (2004) |
| | | Ascorbic acid | approved | Atrial Fibrillation, Stroke | Pilei et al. (2013); Wang et al. (2013) |
| | | Bexarotene | approved | Cutaneous T-Cell Lymphoma, Mycosis Fungoides | Del Rosso, (2020); Choi et al. (2017) |
| | | Clobetasol propionate | approved | Psoriasis | Eleutherakis-Papaioikou et al. (2019); Ki et al. (2005) |
| | | Dexamethasone | approved | Multiple Myeloma | Jain et al. (2021); Tsuchida et al. (2017) |
| | | Halofuginone | investigative | Fibrosis | Chen et al. (2020c); Tarumoto et al. (2004) |
| | | Luteolin | investigative | Neoplasm | Franz et al. (2021); Tang et al. (2011) |
| | | AEM1 | experimental | Neoplasm | Hoffmann et al. (2014); Bollong et al. (2015) |
| | | Brusatol | experimental | Neoplasm | Xie et al. (2021); Ren et al. (2011) |
| | | Malabaricone-A | experimental | Leukemia | Manna et al. (2015) |
| | | Ochratoxin A | experimental | Kidney Diseases (idiopathic) | Lymoncelli and Jannings, (2014) |
| | | Trigonelline | experimental | Diabetes Mellitus | Artt et al. (2013) |
| | | Wogonin | experimental | Neoplasm | Huynh et al. (2020); Zhong et al. (2013) |
| | | Lycopene | approved | Adrenal Cortex Diseases, Prostate Neoplasm, Atherosclerosis | Mirahmadi et al. (2020); Costa-Rodrigues et al. (2018) |
| | | Andrographolide | investigational | Ulcerative Colitis | Paul et al. (2021) |
| | | Rosmarinic acid | investigational | Cerebral Hemorrhage, Extrahepatic Cholestasis, Encephalomalacia, Nervous System Disorders | Ghasemzadeh and Hosseinzadeh, (2020) |
| | | L-F001 | experimental | CNS Inflammation | Chen et al., (2017) |
| | | 3H-1,2-Dithiole-3-thione | experimental | Neoplasm | Park et al. (2008) |
| Keap1 modification | Keap1 | Beta carotene | approved | Reduction of Photosensitivity in patients with Erythropoietic Protoporphyria and other Photosensitivity Diseases, Muscular Degeneration | Johra et al. (2020); Pricci et al. (2020); Lo Cascio et al. (2021) |
| | | Curcumin | approved | Pediatric Ulcerative Colitis, Neurodegenerative Disease, Vascular Dysfunction | Li et al. (2014); Li et al. (2018) |
| | | Pumblagin | investigational | Metastatic Castration-Resistant Prostate Cancer | Yin et al. (2020) |
| | | Tert-butylhydroquinone | investigational | Hepatoocellular Carcinoma, Acne Vulgaris | Li et al. (2014) |
| | | Ally sulfide | experimental | Hepatitis | Li et al. (2018) |
| | | Graveolene | experimental | Phototoxic Dermatitis | Sampaio et al. (2018) |
| | | Tetrahydroisoquinoline | experimental | Parkinson Disease | Ane et al. (2005); Richardson et al. (2015); Jhoff et al. (2014) |
| | | Thiopyrimidine | experimental | Neoplasm | Syam et al. (2019); Marzotto et al. (2013) |
| Nrf2 activator | | Caffeine | approved | Neoplasm | Bors et al. (2018) |
| | | Cinnamaldehyde | approved | Neoplasm | Aminzadeh et al. (2021) |
| | | Dimethyl fumarate | approved | Relapsing Remitting Multiple Sclerosis | Valencia-Sanchez and Carter, (2020) |
| | | Ethyl ferulate | approved | Alzheimer Disease, Inflammation | Wu et al. (2021); Mohmmad Abdul and Butterfield, (2005) |
| | | Ferric pyrophosphate citrate | approved | Iron Deficiency, Enemia | Mazgaj et al. (2020) |
| | | Bardofoxolone | investigational | Neoplasm | Ju et al. (2021) |
| | | Bardofoxolone methyl | investigational | Neoplasm | Chien et al. (2021) |
| | | Epigallocatechin gallate | investigational | Neoplasm | Tauber et al. (2020); Jaiswal et al. (2019); Bhat et al. (2021) |
| | | Paeonol | investigational | Prostate Neoplasm, Breast Neoplasm, Atherosclerosis, Hepatocellular Carcinoma | Veilasamy et al. (2021); Chen et al. (2012) |
| | | Phenethyl isothiocyanate | investigational | Leukemia, Lung Cancer, Lymphoproliferative Disorders | Wang et al. (2018); Sun et al. (2019); Gupta et al. (2014) |
| | | Piperine | investigational | Neoplasm, COVID-19 | Quijia and Chorilli, (2021); Miryan et al. (2021) |
| | | Quercetin | investigational | Neoplasm | Zhao et al. (2021); Zang et al. (2021) |
| | | Xanthohumol | investigational | Breast Neoplasm, Hepatocellular-Carcinoma, Colorectal Neoplasms, Lymphatic Metastasis | Gieroba et al. (2020); Seitz et al. (2021); Krajka-Kuniak et al. (2013) |
| | | Bacipan | experimental | Brain Ischemia, Hepatitis B | Liang et al. (2017); Yang et al. (2021) |
| | | Caffeic acid phenethyl ester | experimental | Neoplasm | Lv et al. (2021) |
| | | Carnosic acid | experimental | Mitochondrial Diseases | de Oliveira, (2018) |
cascade phosphorylation, thus transmitting the upstream signal to the downstream response molecules, which in turn are involved in the cellular anti-stress and anti-inflammatory responses. MAPKs signaling pathways play an important role in mediating cellular responses, and are widely involved in cell growth and reproduction, apoptosis, and a variety of cellular biochemical reactions. The pathways mediated by these four isoforms (JNK pathway, p38MAPK pathway, MEK5/ERK5 pathway, and ERK1/ERK2 pathway) are widely involved in the inflammatory, oxidative stress, and extracellular metabolic responses of cells in the body. ERK is one of the first MAPK isoforms to be identified and has five isoforms (ERK1 to ERK5), among which ERK1 and ERK2 are the most intensively studied and have a high degree of homology (Guo et al., 2008). The signaling pathway mediated by ERK1/ERK2 is mainly a signaling axis consisting of Ras, Raf, MEK, and ERK, through which upstream signals are transmitted step by step, leading to the regulation of multiple downstream genes, ultimately leading to the regulation of multiple genes downstream. In normal resting cells, Ras binds to GDP in an inactive state, while when the cell is stimulated by the outside world, Ras binds to GTP, which has one more phosphate group than GDP, and converts to an active state. The extra growth substrate puts the two switches (threonine-35 and glycine-60) in a “load spring” state, and when the phosphate group is released, the switch site shifts back to the inactive state (Santarpia et al., 2012). Ras-GTP induces Raf binding to Ras, mobilizes inactive proteins in the cytoplasm, and causes Raf kinase to accumulate at the cytosolic membrane (Chong et al., 2003; Wellbrock et al., 2004). When the Ras-Raf complex reaches the cell membrane, Ras can activate the function of the Raf isoform of serine/threonine kinase. When the Ras-Raf complex reaches the cell membrane, Ras activates the function of the Raf isoform of serine/threonine kinase. Activated Raf with its C-terminal catalytic region binds to MEK, phosphorylating the two serines (Ser221 and Ser217) in its subregion and activating MEK. Activated MEK can in turn phosphorylate the dual threonine and tyrosine sites on ERK, which activates ERK (Tyr183 and Tyr185 for ERK1 phosphorylation sites and Tyr202 and Tyr204 for ERK2 phosphorylation sites). ERK1 and ERK2 are activated for nuclear translocation and regulate many effector genes that will be relevant to cell proliferation, differentiation, survival, growth, and angiogenesis (Crews et al., 1992; Meloche and Pouysségur, 2007; Mebratu and Tesfaigzi, 2009). The ERK5 pathway, also known as the BMK1 pathway, can be activated by epidermal growth factors and a variety of extracellular stimuli, including hyperosmolarity, hypoxia, oxidants, and fluid shear stress. Tyr218 and Tyr220 on ERK5 are activated by regulation of the upstream protein kinase MAPK5, which, like ERK1 and ERK2, undergoes nuclear translocation and regulates the corresponding genes regulation (Figure 5). The ERK5 pathway is also important for cell proliferation and differentiation and organogenesis. For example, Sohn et al. showed that it is ERK5, but not ERK1/2, that plays a key role in the developmental maturation of thymocytes, revealing that ERK5 has a role in mediating the differentiation of T lymphocytes (Sohn et al., 2008). The c-Jun amino-terminal transferase (JNK) was discovered during the study of a series of biological processes (UV responses) in cells exposed to ultraviolet radiation (UV), and it mainly regulates the phosphorylation of activated proteins such as c-Jun (Devary et al., 1992). The JNK pathway is activated after cells are exposed to various biotic or abiotic stress events, such as infection, inflammation, oxidative and other stresses, DNA damage, osmotic stress, or cytoskeletal changes (Zeke et al., 2016). In addition, G proteins such as Rac, CDC-42, tumor necrosis factor receptor-associated factor-based bridging proteins, and death-effector domain-containing proteins can also regulate JNK activation (Schattenberg et al., 2012). MAPK is activated by MAPK kinases (MKKs, MEKs, JNKs, MAP2ks), which are activated by M KK kinases (MEKKs, MAPKKKs, MAP3ks). The first MAP3K found to activate JNK was MEKK1 (Minden et al., 1994). Subsequently, MEKK2 and MEKK3, MEKK4, mixed family kinases 2 and 3 (MLK2, MLK3), double leucine pull chain kinase (DLK), tumor transposon-2 (Tpl-2), TGF-β activating kinase (TAK1), apoptosis signaling regulatory proteases 1 and 2 (ASK1, ASK2), and 1001 amino acid kinases 1 and 2 (Tao1, Tao2) were identified (Karim and Gallagher, 2005). The two MAP2ks specific to the JNK pathway are MKK4 and MKK7, with MKK4 more likely to phosphorylate the 185th tyrosine residue of JNK, while MKK7 prefers the JNK pathway.
et al., 1998). After JNK is activated, it then activates numerous downstream substrates that are involved in numerous intracellular functions, including apoptosis, cytoskeletal reorganization, transcriptional activity, and universal proteinization (Chen et al., 2001). The most common p38MAPK activators are lipopolysaccharides, in addition to osmotic stress, oxidative stress, UV exposure, heat shock, hypoxia, ischemia, interleukin-1β (IL-1β), tumor necrosis factor-α (TNF-α), and transforming growth factor-β (TGF-β), and neuropathic pain (Koul et al., 2013). Unlike the JNK

FIGURE 5 | Mechanistic map of the classical and ERK5 MAPK signaling pathway. c-Myc, cell-myc; EGF, epidermal growth factor; Elk-1, ETS domain-containing protein Elk-1; ERK, extracellular regulated protein kinases; GDP, guanosine diphosphate; GTP, guanosine triphosphate; GRB2, growth factor receptor-bound protein 2; MEK, mitogen-activated protein kinase kinase; MKP, mitogen-activated protein kinase phosphatase1; Nur77, nerve growth factor-induced gene B; PKC, protein kinase C; PTP, protein tyrosine phosphatase; Ras, rennin angiotensin system; RTK, receptor tyrosine kinases; SHC, Src homology 2 domain containing; SOS, son of sevenless. The figure is created with BioRender.com.
FIGURE 6 | Mechanistic map of the JNK and p38 MAPK signaling pathway. Ask1, apoptosis signal-regulating kinase 1; Cdc42, cell division cycle 42; DAXX, death domain-associated protein; Elk-1, ETS domain-containing protein Elk-1; Fas, fatty acid synthase; GLK, glucokinase; HGK, human glandular kallikrein; HPK, histidine protein kinases; JNK, c-Jun N-terminal kinase; MAPKAPK, mitogen activated protein kinase activated protein kinase; MLK, mixed lineage kinase; MNK, mitogen-activated protein kinase interacting kinase; PAK, p21-activated kinase; Rac, Ras-related C3 botulinum substrate; RIP, receptor-interacting protein; TGFβ, transforming growth factor; TRADD, TNF receptor-associated death domain; TRAF, tumor necrosis factor receptor associated factor. The figure is created with BioRender.com.
| Target | Agent | Phase | Indication | References |
|--------|--------|-------|------------|------------|
| Ras processing | Lonafarnib | approved | Hutchinson-Gilford Progeria Syndrome, colorectal cancer, Leukemia (myeloid), Pancreatic Cancer, Solid Tumors | Moore et al. (2020) |
| | Tipifarnib | investigational | | Moore et al. (2020) |
| | Cysmethylamine | experimental | Malignant Pleural Effusion, Neoplasm | Winter-Vann et al. (2005) |
| | Deltarasin | experimental | Adenocarcinoma, Neoplasm | Zimmermann et al. (2013) |
| | NHTD | experimental | Neoplasm | Leung et al. (2019) |
| | UCM-1336 | experimental | Neoplasm | Marin-Ramos et al. (2019) |
| KRAS-G12C | Sotorasib | approved | KRAS G12C mutant Non Small Cell Lung Cancer, Colorectal Cancer, Appendix Cancer, Adenocarcinomas | Hallin et al. (2020) |
| | JNJ-74699157 | investigational | Advance Solid Tumor | Janes et al. (2018) |
| | LYS499446 | investigational | Advance Solid Tumor | Uprety and Adjei, (2020) |
| | ARS-1620 | experimental | Neoplasm | Patrocelli et al. (2016) |
| | Sulindac | approved | Osteoarthritis, Rheumatoid Arthritis, Ankylosing Spondylitis, Acute Painful Shoulder, Acute Gouty Arthritis | O’Bryan Pharmacological targeting of RAS, (2019) |
| | BI-2852 | experimental | Neoplasm | O’Bryan Pharmacological targeting of RAS, (2019) |
| | DCAI | experimental | Heart Disease | O’Bryan Pharmacological targeting of RAS, (2019) |
| | Kobe0065 | experimental | Colonic Neoplasm, Colorectal Neoplasm | O’Bryan Pharmacological targeting of RAS, (2019) |
| SOS | BAY-293 | experimental | Neoplasm, Non-Small-Cell Lung Carcinoma | Hillig et al. (2019) |
| | Bi-3406 | experimental | Non-Small-Cell Lung Carcinoma | Karoula et al. (2016) |
| | Bi-1701963 | investigational | Advanced and Metastatic Solid Tumor | Karoula et al. (2016) |
| | JAB-3068 | investigational | Advance Solid Tumor | Karoula et al. (2016) |
| | TNO155 | investigational | Advance Solid Tumor | Karoula et al. (2016) |
| | RMC-4550 | experimental | Neoplasm, Neuroblastoma | Nicholas et al. (2018) |
| Raf | Dabrafenib | approved | Specific types of Melanoma, Non-Small Cell Lung Cancer, Thyroid Cancer | Karoula et al. (2016) |
| | Encorafenib | approved | Unresectable or Metastatic Melanoma with specific mutations | Karoula et al. (2016) |
| | Sorafenib | approved | Unresectable Liver Carcinoma, Advanced Renal Carcinoma | Karoula et al. (2016) |
| | Vemurafenib | approved | Metastatic Melanoma | Karoula et al. (2016) |
| | Belvarafenib | investigational | Neoplasm, Melanoma | Nicholas et al. (2018); Kim, (2019) |
| | LXH-254 | investigational | Neoplasm, Non-Small-Cell Lung Carcinoma | Nicholas et al. (2018) |
| | LY3099120 | investigational | Neoplasm, Melanoma | Monaco, (2019) |
| | PLX8394 | investigational | Advanced Unresectable Solid Tumors | Karoula et al. (2016) |
| | AZ-628 | experimental | Neoplasm, Melanoma | (Vakana et al., 1202017) |
| | TAK632 | experimental | Systemic Inflammatory Response Syndrome, Melanoma, Neurodegenerative Diseases | Nakamura et al. (2013); Okar et al. (2013) |
| MEK1 | Selumetinib | approved | Several types of Cancer | Lee and Duesbery, (2010) |
| | HL-085 | investigational | Cancer | Tian et al. (2013) |
| | RO4987655 | investigational | Neoplasm | Cheng and Tian, (2017) |
| | G-573 | experimental | Neoplasm | Cheng and Tian, (2017) |
| | PD318088 | experimental | Neoplasm | Cheng and Tian, (2017) |
| MEK5 | BIX02188 | experimental | Neuroagia, Substance Withdrawal Syndrome | Drew et al. (2012) |
| | BIX02189 | experimental | Cardiomegaly, Acute Myeloid Leukemia | Drew et al. (2012) |
| | Binimetinib | approved | Metastatic Melanoma with specific mutations | Pheong et al. (2009) |
| | Cobimetinib | approved | Unresectable or Metastatic Melanoma | Cheng and Tian, (2017) |
| | Trametinib | approved | Specific types of Melanoma, Non-Small Cell Lung Cancer, Thyroid Cancer | Cheng and Tian, (2017) |
| MEK1/MEK2 | AZD-8330 | investigational | Advance Solid Tumor | Wallace et al. (2009) |
| | C1-1040 | investigational | Breast Cancer, Colorectal Cancer, Lung Cancer, Pancreatic Cancer | Barrett et al. (2008) |
| | GDC-0923 | investigational | Metastatic Solid Tumors | Hatzivassiliou et al. (2013) |
| | PD-0325901 | investigational | Melanoma, Solid Tumors, Advanced Cancer, Breast Neoplasm | Barrett et al. (2008) |
| | Pimasertib | investigational | N-Ras Mutated Locally Advanced or Metastasis Malignant Cutaneous Melanoma, Ovarian Cancer | Cheng and Tian, (2017) |

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# TABLE 5 | (Continued) Targets in and inhibitor targeting the MAPK pathway.

| Target       | Agent           | Phase        | Indication                                                                 | References                                                                 |
|--------------|-----------------|--------------|----------------------------------------------------------------------------|----------------------------------------------------------------------------|
| Refametinib  | investigational | Hepatocellular Cancer, Melanoma, Colorectal Cancer | Iverson et al. (2009)                                                      |                                                                            |
| TAK733       | investigational | Advanced Non-Hematologic Malignancies Advanced Metastatic Melanoma | Dong et al. (2011)                                                        |                                                                            |
| WX-554       | investigational | Fibrosisarcoma, Sarcoma, Neoplasm                     | Jamieson et al. (2018)                                                     |                                                                            |
| ClnQ-03      | experimental    | Hepatocellular Carcinoma, Neoplasm                    | Cheng and Tian (2017)                                                      |                                                                            |
| PD184161     | experimental    | Hyperalgesia, Edema, Hypertrophy                      | Cheng and Tian (2017)                                                      |                                                                            |
| PD08059      | experimental    | Neoplasm, Melanoma                                     | Ishii et al. (2011)                                                        |                                                                            |
| SL327        | experimental    | Drug-Induced Dyskinesia, Cocaine-Related Disorders     | Cheng and Tian (2017)                                                      |                                                                            |
| Raf/MEK1/MEK2| investigational | Neoplasm                                               | Ishii et al. (2011)                                                        |                                                                            |
| ERK          | CC-90003        | investigational | Mesenteric Ischemia, Peripheral Nervous System Diseases | Kidger et al. (2018)                                                      |
| ERK inhibitor| KO-947          | investigational | Non-Small Cell Lung Cancer                                      | Kidger et al. (2018)                                                      |
| ERK          | LTT462          | investigational | Unresectable or Metastatic Melanoma                              | Kidger et al. (2018)                                                      |
| ERK          | LY-3214966      | investigational | Neoplasm, Melanoma                                              | Kidger et al. (2018)                                                      |
| ERK          | MK-8353         | investigational | Neoplasm, Melanoma, Chronic Brain Damage                        | Kidger et al. (2018)                                                      |
| ERK          | Raxertinib      | investigational | Locally Advanced or Metastatic Solid Tumors                     | Kidger et al. (2018)                                                      |
| ERK          | Ulterertinb     | investigational | Tumor                                                      | Kidger et al. (2018)                                                      |
| ERK          | DEL-22379       | experimental  | Neoplasm                                                      | Kidger et al. (2018)                                                      |
| ERK          | FR180204        | experimental  | Neoplasm                                                      | Kidger et al. (2018)                                                      |
| ERK          | Vtx-11e         | experimental  | Neoplasm, Retinoblastoma                                        | Kidger et al. (2018)                                                      |
| ERK5         | XMD6-92         | experimental  | Neoplasm, Myelodysplasia                                       | Drew et al. (2012)                                                       |
| p38          | ARYR37197       | investigational | Dilated Cardiomyopathy                                   | Banerjee et al. (2012)                                                    |
| p38          | BIBR 796        | investigational | Chemical and Drug Induced Liver Injury, Crohn Disease         | Bagley et al. (2010)                                                      |
| p38          | BMS582894       | investigational | Rheumatoid Arthritis, Inflammation                           | Banerjee et al. (2012)                                                    |
| p38          | Panamipmod      | investigational | Osteoporosis, Rheumatoid Arthritis                          | Banerjee et al. (2012)                                                    |
| p38          | PF03715455      | investigational | Chronic Obstructive Pulmonary Disease                         | Banerjee et al. (2012)                                                    |
| p38          | PH797804        | investigational | Pulmonary Disease, Chronic Obstructive                        | Banerjee et al. (2012)                                                    |
| p38          | SB681323        | investigational | Pulmonary Disease, Chronic Obstructive                        | Banerjee et al. (2012)                                                    |
| p38          | VX745           | investigational | Werner Syndrome, Rheumatoid Arthritis                        | Banerjee et al. (2012)                                                    |
| p38          | SB203580        | experimental  | Cardiomyopathies, Chemical and Drug Induced Liver Injury       | Banerjee et al. (2012)                                                    |
| p38          | SB239063        | experimental  | Middle Cerebral Artery Infarction                             | Banerjee et al. (2012)                                                    |
| p38          | SB706504        | experimental  | Chronic Obstructive Pulmonary Disease                         | Banerjee et al. (2012)                                                    |
| p38          | SD3006          | experimental  | Arthritis, Rheumatoid Arthritis                               | Banerjee et al. (2012)                                                    |
| p38          | RO2201195       | experimental  | Werner Syndrome                                               | Bagley et al. (2010)                                                      |
| p38          | URI-13756       | experimental  | Werner Syndrome                                               | Bagley et al. (2010)                                                      |
| ASK1         | Selonsertib     | investigational | Nonalcoholic Steatohepatitis, Bridging (F3) Fibrosis         | (Rosenkranz et al., 2017; Schuster et al., 2017; Loomba et al., 2018; Yoonossi et al., 2018; Chertow et al., 2019; Ji et al., 2019) |
| ASK1         | BPY-O-34        | experimental  | Autoimmune Disorders, Cancer                                  | Starosy et al. (2015)                                                     |
| ASK1         | GS-44217        | experimental  | Fibrosis, Glomerulonephritis, Inflammation                    | (Tesch et al., 2015; Amos et al., 2018; Budas et al., 2018; Lies et al., 2018) |
| ASK1         | GS-459679       | experimental  | Liver Injury                                                   | He et al. (2016); Xie et al. (2015); Gerczek et al. (2012)                |
| ASK1         | GS-627          | experimental  | Arthritis, Inflammation                                       | Nygaard et al. (2018)                                                    |
| ASK1         | MSC2032964A     | experimental  | Neurodegenerative Diseases, Cardiovascular Diseases          | Guo et al. (2010)                                                        |
| TC ASK 10    | experimental    | Chronic Obstructive Pulmonary Disease                  | Eapen et al. (2018); Terao et al. (2012)                                 |
| JNK1         | AV-7            | experimental  | Diabetes                                                      | Yao et al. (2009)                                                        |
| JNK1         | Isoquinolone derivatives | experimental | Heart Failure                                                | Asano et al. (2008)                                                      |
| JNK3         | PYC71N          | experimental  | Hyperosmotic Stress                                           | Haynes et al. (2012); Ngoei et al. (2011)                                  |
| JNK3         | PYC98           | experimental  | Hyperosmotic Stress                                           | Haynes et al. (2012); Ngoei et al. (2011)                                  |
| JNK3         | Brimapitide     | experimental  | Infarction, Nerve Degeneration                                 | Beydoun et al. (2015); Desire et al. (2018)                               |
| JNK3         | experimental    | No Data                                                  | Zhao et al. (2012)                                                        |

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pathway, p38 is mainly activated by two MAPKKs, MKK3 and MKK6, and activation of p38 requires simultaneous dual phosphorylation of threonine and tyrosine. As mentioned before G proteins such as Rac, CDC-42 can activate the JNK pathway, and its activation of p38 is also promoted. Rac1 can bind to MEKK1 or MLK1, while Cdc42 can only bind to MLK1, both of which can lead to the activation of p38 through MAP3Ks (Tibbles et al., 1996; Hirai et al., 1997). p38 then nuclear translocates and acts on downstream substrates, which include a large number of transcription factors such as activated transcription factors 1, 2 and 6 (ATF-1/2/6), SRF accessory protein (Sap), CHOP (growth arrest and DNA damage inducible gene 153, or GADD153), p53, C/EBPβ, myocyte enhancer factor 2C (MEF2C) MEF2A, MITF1, DDIT3, ELK1, NFAT, and high mobility histone box protein 1 (HBP1) (Zarubin and Han, 2005) (Figure 6). Due to the complexity of the MAPK signaling pathway, resulting in a wealth of targets for its action, researchers have so far conducted a lot of research and development on inhibitors of various targets on this pathway. Table 5 shows a summary of

| Target          | Agent                  | Phase   | Indication                                      | References                                                                 |
|-----------------|------------------------|---------|------------------------------------------------|---------------------------------------------------------------------------|
| Pyridopyrimidine derivatives |                        |         |                                                |                                                                           |
| Quinazoline     |                        |         |                                                |                                                                           |
| Trizolothione 1 |                        |         |                                                |                                                                           |
| 6-anilinodiazole |                        |         |                                                |                                                                           |
| 20-anilin-4,40-bipyridines |                  |         |                                                |                                                                           |
| JNK1/JNK2       | 4-quinolone analogues  | experimental | Asthma                                      | Gong et al. (2012)                                                        |
| JNK1/JNK3       | 4-fluorophenyl isoxazoles |         |                                                |                                                                           |
| JNK1/JNK2/JNK3  | Bentamapimod           |         |                                                |                                                                           |
| CC-401          |                        |         |                                                |                                                                           |
| CC-930          |                        |         |                                                |                                                                           |
| AS601245        |                        |         |                                                |                                                                           |
| BL-78D3         |                        |         |                                                |                                                                           |
| Ginsenoside Rg1 |                        |         |                                                |                                                                           |
| JNK-IN-1        |                        |         |                                                |                                                                           |
| JNK-IN-8        |                        |         |                                                |                                                                           |
| Pyrazolanthrone  |                        |         |                                                |                                                                           |
| MNK inhibitor   | Cerceporamide           |         |                                                |                                                                           |
| CEP1347         |                        |         |                                                |                                                                           |
| CEP11004        |                        |         |                                                |                                                                           |
| K252a           |                        |         |                                                |                                                                           |
| MLK inhibitor   | CEP1347                |         |                                                |                                                                           |
| CEP11004        |                        |         |                                                |                                                                           |
| K252a           |                        |         |                                                |                                                                           |
| PKC inhibitor   | Isopropyl myristate     | approved|                                              |                                                                           |
| Enzastaurin     |                        |         |                                                |                                                                           |
| Ruboxistaurin   |                        |         |                                                |                                                                           |
| Sotrastaurin    |                        |         |                                                |                                                                           |
| Calphostin C    |                        |         |                                                |                                                                           |
| Chelerythrine   |                        |         |                                                |                                                                           |
| GF 109203X      |                        |         |                                                |                                                                           |
| Rotterlin       |                        |         |                                                |                                                                           |
| Ro 31–8220      |                        |         |                                                |                                                                           |
| Staurosporine   |                        |         |                                                |                                                                           |

Table 5 | (Continued) Targets in and inhibitor targeting the MAPK pathway.
some of the targeted inhibitors of the MAPK pathway, with a list of their indications and stages of research.

Sulindac is an FDA-approved drug for the treatment of autoimmune diseases such as rheumatoid arthritis that blocks the MAPK pathway and whose primary target is HRAs (one of four highly homologous proteins encoded by the Ras gene) (O’Bryan Pharmacological targeting of RAS, 2019). Subsequently, it was shown that sulforaphane sulfide, a metabolite of sulforaphane, could directly block Ras activation of Raf and reduce Ras-mediated transformation in vitro (Herrmann et al., 1998). Of course, sulforaphane does not only act on one pathway, but it can also exert its effects by inhibiting the NF-κB pathway, which has been shown to inhibit NF-κB activation by binding to the ATP-binding site of IKK and regulating RelA nuclear translocation (Berman et al., 2002). Approximately 93% of sulindac and the prototype drug and 98% of the sulfated metabolites are bound to serum albumin after oral administration, with the liver being an important elimination pathway. Currently, approximately 50% of sulindac is excreted in the urine, and studies have found that sulindac can be excreted from rat milk, while it is debatable whether it can be excreted from human milk. Between the complexity of Ras targeting and the fact that the Ras family is one of the most commonly mutated genes in tumor cancers, researchers have put a great deal of effort into the family. Until a decade ago, researchers had not found an effective Ras inhibitor, so much so that Ras was used as an ineffective therapeutic target. However, after nearly 3 decades of research, a breakthrough in Ras inhibitor research has emerged and tremendous progress has been made to date, with tremendous scope for research. The first Ras inhibitor to enter clinical trials was AMG510, which has now been cleared by the FDA for marketing. It was found that the target of action is mainly KRAS-G12C, which can be covalently inhibited by cysteine at codon 12 of the gene, whereas wild-type KRAS does not have covalently bindable cysteine specifically, so AMG510 is a specific target drug for this commonly mutated region of G12C (Moore et al., 2020). Subsequently, researchers have identified other Ras inhibitors that are partially in clinical trials, such as Adagrasib, INJ-74699157, and LY3499446, while some are still in the preclinical study evaluation stage and have not entered clinical trials or marketing, such as ARS-853 and ARS-1620. In addition to the target KRAS-G12C, Shokat et al. identified and defined for the first time a metamorphic binding pocket located in the switch-II region of the G12C mutation, for which they designed a series of irreversible inhibitory compounds that resulted in a good inhibitory effect on the pathway (Ostrem et al., 2013), thus showing a new research direction and a good research prospect for Ras inhibitors.

Although the treatment of cancer patients or patients with neurodegenerative lesions with inhibitors targeting this pathway has shown a good trend of prolonged survival and good improvement of lesion symptoms, these inhibitors still inevitably cause side effects. For example, Stephnie et al. reported that patients treated with the MEK inhibitor trametinib for melanoma experienced prolonged visual loss that did not completely resolve after discontinuation of the drug and could even progress to extensive uveitis and multiple plasmacytoid retinal detachments (Sarny et al., 2017). The mechanism of the complication of this ocular side effect cannot be elucidated at this time, but physicians and pharmacists are cautioned to use the medication carefully and to adjust it within the therapeutic window. In addition to this, in a study of the patient population when trametinib was combined with dabrafenib in the treatment of non-small cell lung cancer, it was found that most patients experienced systemic adverse effects such as fever, skin inflammation, mouth ulcers, diarrhea, and loss of appetite (Chalmers et al., 2019), but this was mainly less related to the inhibition of the MAPK pathway and more due to drug metabolites or drug. This is less related to MAPK pathway inhibition and more to pathological changes caused by drug metabolites or drugs themselves. However, this is also a warning to physicians and pharmacists to master the balance between the therapeutic effects of drugs and adverse drug reactions.

CONCLUSION

This article reviews representative targets and their inhibitors on the JAK-STAT, NF-κB, PI3K-AKT-mTOR, MAPK, and Keap1-Nrf2-ARE pathways, and indicates their current research stages and indications, thus facilitating researchers to conduct in-depth comparative studies on drugs with the same targets. A large number of studies and clinical observations have demonstrated the efficacy of targeted immunosuppressive agents in chronic inflammatory diseases, but a variety of adverse effects or ethical issues have resulted in relatively few marketed drugs for human use, and most of the drugs found to be effective have been forced to end up in clinical trials or preclinical studies. Researchers are now working to find commonalities between immunosuppressive agents of the same target and to study the structural similarities of the drugs, thus facilitating further development work on the target molecules. In addition to this, researchers face the challenge of studying the targeting of drugs to specific cells or tissues, i.e. the detailed study of the pharmacokinetics of a particular drug. It is hoped that the therapeutic potential and safety of small molecule immunosuppressive agents/targeted therapy immunosuppressive agents will be further demonstrated and evaluated to achieve more interventions, improvements and treatments for chronic diseases.

Although the widespread use of immunosuppressive agents has solved many problems in autoimmune diseases and organ transplantation, among others, the road to immunosuppression has never stopped. Currently, the world is still facing a shortage of donor organs for transplantation, which will mean that we will need to find xenogeneic donors, such as pigs, thus alleviating the lack of donors. For example, today porcine xenografts and hepatocyte transplants are gradually being classified into human treatment options for liver diseases. However, it has been
found that xenografted porcine grafts can cause many adverse reactions such as rejection, coagulation disorders, and thrombocytopenia while performing a liver support role (Li et al., 2022). Even with porcine modified donor livers (PERV-KO/3-KO/9-TG), humoral rejection, interstitial hemorrhage, and inflammatory injury still occur. Therefore, the focus of transplantation is now more towards porcine allogeneic hepatocyte transplantation. The lower immunogenicity of genetically modified porcine hepatocytes has led to a much higher success rate of transplantation, and it is hypothesized that the key to successful cellular xenotransplantation is related to the source of blood for liver perfusion. In contrast to whole organs that are perfused by the donor’s vessels, the blood supply for cellular grafts originates from the recipient (Parker et al., 1996; Cascalho and Platt, 2001). Although the success rate of surgery is gradually improving, there is still a need to pursue more efficient immunosuppression combined with more excellent genetic modification protocols, which can not only solve the problem from the donor, but also improve the prognostic quality of the recipient in the postoperative period. This raises thoughts and requirements for in-depth development and flexible combination applications of immunosuppressive agents.

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**REFERENCES**

Abe, K., Saitoh, T., Horiguchi, Y., Utsumoniya, I., and Taguchi, K. (2005). Synthesis and Neurotoxicity of Tetrahydrosoquinoaline Derivatives for Studying Parkinson’s Disease. *Bioll. Pharm. Bull.* 28 (8), 1355–1362. doi:10.1248/bpb.28.1355

Agrawal, M., Kim, E. S., and Colombel, J. F. (2020). JAK Inhibitors Safety in Ulcerative Colitis: Practical Implications. *J. Crohns Colitis 14*, 5755–5760. doi:10.1093/ecto-jcc/jaa017

Alfonso, L., Ai, G., Spite, R. C., and Bhat, G. J. (2014). Molecular Targets of Aspirin and Cancer Prevention. *Br. J. Cancer* 111, 61–67. doi:10.1038/bjc.2014.271

Alhazzani, K., Ahmad, S. F., Al-Harbi, N. O., Attia, S. M., Bakheet, S. A., Sarawi, W., et al. (2021). Pharmacological Inhibition of STAT3 by Statitic Ameliorates Clinical Symptoms and Reduces Autoinflammation in Myeloid, Lymphoid, and Neuronal Tissue Compartment in Relapsing-Remitting Model of Aspiration and Prevention. *Br. J. Cancer* 111, 61–67. doi:10.1038/bjc.2014.271

Amos, L. A., Ma, F. Y., Tesch, G. H., Liles, J. T., Breckenridge, D. G., Nikolic-Paterson, D. J., et al. (2018). ASK1 Inhibitor Treatment Suppresses P38/JNK Signalling with Reduced Kidney Inflammation and Fibrosis in Rat Crescentic Glomerulonephritis. *J. Cell. Mol. Med.* 22 (9), 4522–4533. doi:10.1111/jcmm.13705

An, J. Y., Pang, H. G., Huang, T. Q., Song, J. N., Li, D. D., Zhao, Y. L., et al. (2018). AG490 Ameliorates Early Brain Injury via Inhibition of JAK2/STAT3-Mediated Regulation of HMGB1 in Subarachnoid Hemorrhage. *Exp. Ther. Med.* 15 (2), 1330–1338. doi:10.3892/etm.2017.5539

Arabi, Y. M., Mandoorah, Y., Al-Hameed, F., Sind, A. A., Almekhlafi, G. A., Hussein, M. A., et al. (2018). Corticosteroid Therapy for Critically Ill Patients with Middle East Respiratory Syndrome. *Am. J. Respir. Crit. Care Med.* 197 (6), 757–767. doi:10.1164/rccm.201706-1172OC

Arlt, A., Sebens, S., Krebs, S., Geissmann, C., Grossmann, M., Kruse, M. L., et al. (2013). Inhibition of the NFκB Transcription Factor by the Alkaloid Trigonelline Renders Pancreatic Cancer Cells More Susceptible to Apoptosis through Decreased Proteasomal Gene Expression and Proteasome Activity. *Oncogene* 32 (40), 4825–4835. doi:10.1038/onc.2012.493

Asano, Y., Kitamura, S., Ohra, T., Itoh, F., Kajino, M., Tamura, T., et al. (2008). Discovery, Synthesis and Biological Evaluation of Isooquinolones as Novel and Highly Selective JNK Inhibitors (2). *Bioorg. Med. Chem.* 16 (8), 4699–4714. doi:10.1016/j.bmc.2008.02.028

Avci, A. B., Feist, E., and Burmester, G. R. (2021). The Role of Upacitabinib in the Treatment of Moderate-To-Severe Active Rheumatoid Arthritis. *Ther. Adv. Musculoskelet. Dis.* 13, 13157920X211047662. doi:10.1177/13157920X211047662

Awasthi, N., Rai, V., Chava, S., Nallasamy, P., Kumnammakara, A. B., Bishaye, A., et al. (2019). Targeting IκappaB Kinases for Cancer Therapy. *Semin. Cancer Biol.* 56, 12–24. doi:10.1016/j.semcancer.2018.02.007

Azuma, M., Yamashita, T., Aota, K., Tamatani, T., and Sato, M. (2001). 5-Fluorouracil Suppression of NF-KappaB Is Mediated by the Inhibition of IkappaB Kinase Activity in Human Salivary Gland Cancer Cells. *Biochem. Biophys. Res. Commun.* 282 (1), 292–296. doi:10.1006.bbrc.2001.4571

Ba, W., Xu, Y., Yin, G., Yang, J., Wang, R., Chi, S., et al. (2019). Metformin Inhibits Pro-inflammatory Responses via Targeting Nuclear Factor-Kb in HaCaT Cells. *Cell. Biochem. Funct.* 37 (1), 4–10. doi:10.1002/cbf.3367

Bagley, M. C., Davis, T., Murzian, P. G., Widdowson, C. S., and Kipling, D. (2010). Use of Ph3 MAPK Inhibitors for the Treatment of Werner Syndrome. *Pharm. (Basel) 3* (6), 1842–1872. doi:10.3390/ph3061842

Ballou, L. M., and Lin, R. Z. (2008). Rapsynycin and mTOR Kinase Inhibitors. *J. Chem. Biol.* 1, 27–36. doi:10.12151/s12154-008-0003-5

Banerjee, A. A., Shen, H., Hautman, M., Anwer, J., Hong, S., Kapetanovic, I. M., et al. (2013). Enhanced Oral Bioavailability of the Hydrophobic Chemopreventive Agent (SR13668) in Beagle Dogs. *Curr. Pharm. Biotechnol.* 14 (4), 464–469. doi:10.2174/138920101340040012

Banerjee, A., Kooizol-White, C., and Panettieri, R., Jr. (2012). p38 MAPK Inhibitors, IKK2 Inhibitors, and TNFα Inhibitors in COPD. *Curr. Opin. Pharmacol.* 12 (3), 281–287. doi:10.1016/j.coph.2012.01.016

Barrett, S. D., Bridges, J., Dudley, D. T., Saltiel, A. R., Fergus, J. H., Flamme, C. M., et al. (2008). The Discovery of the Benzhydroxamate MEK Inhibitors CI-1040 and PD 0325901. *Bioorg. Med. Chem. Lett.* 18, 6501–6504. doi:10.1016/j.bmcl.2008.10.054

Bassères, D. S., Ebbs, A., Cogswell, P. C., and Baldwin, A. S. (2014). IKK Is a Therapeutic Target in Kras-Induced Lung Cancer with Disrupted P53 Activity. *Genes. Cancer* 5, 41–55. doi:10.18632/genesandcancer.5

Ben-Neriah, Y., and Karin, M. (2011). Inflammation Meets Cancer, with NF-Kb as the Matchmaker. *Nat. Immunol.* 12 (8), 715–723. doi:10.1038/ni.2060

Berdjaa, J., Palandri, F., Baer, M. R., Quick, D., Kiladjian, J. J., Martellini, G., et al. (2018). Phase 2 Study of Gandotinib (LY2784544) in Patients with
Adhesion Molecule Expression and Reduces the Severity of Dextran Sulfate Sodium-Induced Colitis in Mice. Inflammm. Res. 52, 508–511. doi:10.1007/s00011-003-1206-4
Mades, F., Eisenberg, T., Pietrocola, F., and Kroemer, G. (2018). Spermidines in Health and Disease. Science 359 (6354), eaan2788. doi:10.1126/science.aan2788
Mageh, S., Chen, Y., and Hu, L. (2012). Small Molecule Modulators of Keap1-Nrf2-ARE Pathway as Potential Preventive and Therapeutic Agents. Med. Res. Rev. 32 (4), 687–726. doi:10.1002.med.21257
Mahajan, S., Hogan, J. K., Shlyakhter, D., Oh, L., Salituro, F. G., Farmer, L., et al. (2015). VX-509 (Decernotinib) Is a Potent and Selective Janus Kinase 3 Inhibitor with Potent In Vivo Antitumor Activity. Mol. Cancer Ther. 7, 1851–1863. doi:10.1158/1535-7163.MCT-08-0017
Manna, A., De Sarkar, S., De, S., Bauri, A. K., Chattopadhyay, S., and Chatterjee, M. (2019). Dual Phosphatidylinositol 3-kinase/mammalian Target of Rapamycin Inhibitor: A Tool to Correlate IKK-2 Activity to the Fate and Functions of the Components of the Nuclear Factor-kappaB Pathway in Leukemic and Solid Tumor Cell Lines Depends on the Degree of Redox Imbalance. J. Pharmacol. Exp. Ther. 359 (6374), eaan2788. doi:10.1126/science.aan2788
Mengarda, A. C., Mendonça, P. S., Morais, C. S., Cogo, R. M., Mazloum, S. F., Salvadori, M. C., et al. (2020). Antiparasitic Activity of Piptilartine (Piperlongunine) in a Mouse Model of Schistosomiasis. Acta Trop. 205, 105350. doi:10.1016/j.actatropica.2020.105350
Meyr, D. M., Jesson, M. I., Li, X., Ehrig, M. M., Funckes-Shippy, C. L., Warner, J. D., et al. (2010). Anti-inflammatory Activity and Neutrophil Reductions Mediated by the JAK1/JAK3 Inhibitor, CP-690,550, in Rat Adjuvant-Induced Arthritis. J. Inflamm. (Lond.) 7, 741. doi:10.1186/1476-9255-7-41
Millet, C., Foali, A., Sasaki, K., La Pietra, V., Balzano, A. L., Marinelli, L., et al. (2015). A Novel Cell-Permeable, Selective, and Noncompetitive Inhibitor of KAT3 Histone Acetyltransferases from a Combined Molecular Pruning/ classical Isosterism Approach. J. Med. Chem. 58 (6), 2779–2798. doi:10.1021/jm5019687
Mindén, A., Lin, A., McMahon, M., Lange-Carter, C., Derijard, B., Davis, R. J., et al. (1994). Differential Activation of ERK and JNK Mitogen-Activated Protein Kinases by Raf-1 and MEKK. Science 266 (5191), 1719–1723. doi:10.1126/science.7992057
Mirahmadi, M., Azimi-Hashemi, S., Saburi, E., Kamali, H., Pishbin, M., and Hadizadeh, F. (2020). Potent Inhibitory Effect of Lycopene on Prostate Cancer. Biomed. Pharmacother. 129, 110459. doi:10.1016/j.biopha.2020.110459
Miyar, M., Soleimani, D., Askari, G., Jamialahmadi, T., Guest, P. C., Bagherniya, M., et al. (2021). Curcumin and Piperine in COVID-19: A Promising Duo to the Rescue? Adv. Exp. Med. Biol. 1327, 197–204. doi:10.1007/978-3-030-71697-4_16
Mohammad Abdul, H., and Butterfield, D. A. (2005). Protection against Amyloid Beta-Peptide (1–42)-induced Loss of Phospholipid Asymmetry in Synaptosomal Membranes by Tricyclodec-9–Xanthogenate (D609) and Fuceric Acid Ethyl Ester: Implications for Alzheimer’s Disease. Biochem. Biophys. Acta 1741 (1–2), 140–148. doi:10.1016/j.bbapain.2004.12.002
Molkovskiy, A., and Sui, L. L. (2008). First-in-class, First-In-Human Phase I Results of Targeted Agents: Highlights of the 2008 American Society of Clinical Oncology Meeting. J. Hematol. Oncol. 1, 20. doi:10.1186/1756-8722-1-20
Monaco, K. A. (2019). RAF Inhibitor LHX254 Effectively Inhibits B-And-CRAF, but Not ARAF [abstract]. Cancer Res. 79 (Suppl. 13), 144.
Montilla, A. M., Gómez-García, F., Gómez-Arias, P. J., Gay-Mimbreta, J., Hernández-Parada, J., Isla-Tejera, B., et al. (2019). Scoping Review on the Use of Drugs Targeting JAK/STAT Pathway in Atopic Dermatitis, Vitiligo, and Alopecia Areata. Dermatol. Ther. (Heidelb.) 9 (4), 655–683. doi:10.1186/s13553-019-00329-7
Moore, A. R., Rosenberg, S. C., McCormick, F., and Malek, S. (2020). RAS-Targeted Therapies: Is the Undruggable Drugged?. Nat. Rev. Drug Discov. 19 (8), 533–552. doi:10.1038/s41573-020-0068-6
Moss, N. C., Stansfeld, W. E., Willis, M. S., Tang, R. H., and Selzman, C. H. (2007). IKKβ Inhibition Attenuates Myocardial Injury and Dysfunction Following Acute Ischemia-Reperfusion Injury. Am. J. Physiol. Heart Circ. Physiol. 293, H2248–H2253. doi:10.1152/ajpheart.00776.2007
Munoz, J., follows, G. A., and Nastoupil, L. J. (2021). Capanonisib for the Treatment of Malignant Lymphoma: Clinical Experience and Future Perspectives. Target Oncol. 16 (3), 295–308. doi:10.1007/s11523-021-00802-9
Muslin, F. Z., and Cristina, R. T. (2019). Homeostatic Changes of Some Trace Elements in Newborn Piglets. J. Trace Elem. Med. Biol. 6046. doi:10.1021/acs.jmedchem.9b00145
Nagin, S., Nivetha, R., and Palarsu, M. Neem Limonoid (2021). Nimbolide, a Neem Secondary Metabolite of Biological Potency. J. Med. Chem. 48, 2652–2659. doi:10.1021/acs.jmedchem.0c02239
Nakamura, A., Arita, T., Tsuchiya, S., Donelan, J., Chouitrat, J., Carideo, E., et al. (2013). Antitumor Activity of the Selective Pan-Raf Inhibitor TAK-632 in BRAF Inhibitor-Resistant Melanoma. Cancer Res. 73 (23), 7043–7055. doi:10.1158/0008-5472.CAN-13-1825
Quintas-Cardama, A., and Verstovsek, S. (2013). Molecular Pathways: Jak/STAT Pathway: Mutations, Inhibitors, and Resistance. Clin. Cancer Res. 19 (8), 1933–1940. doi:10.1158/1078-0432.CCR-12-0284

Rajendrasozhan, S., Hwang, J. W., Yao, H., Kishore, N., and Rahman, I. (2010). Anti-inflammatory Effect of a Selective IkappaB Kinase-Beta Inhibitor in Rat Lung in Response to LPS and Cigarette Smoke. Palm. Pharmacol. Ther. 23, 172–181. doi:10.1016/j.pjpt.2010.01.002

Reilly, S. M., Chiang, S. H., Decker, S. J., Chang, L., Uhm, M., Larsen, M. J., et al. (2013). An Inhibitor of the Protein Kinasas TBK1 and IKK-E Improves Obesity-Related Metabolic Dysfunctions in Mice. Nat. Med. 19 (3), 313–321. doi:10.1038/nm.3082

Ren, D., Villeneuve, N. F., Jiang, T., Wu, T., Lau, A., Toppin, H. A., et al. (2011). Brusatol Enhances the Efficacy of Chemotherapy by Inhibiting the Nrf2-Mediated Defense Mechanism. Proc. Natl. Acad. Sci. U. S. A. 108 (4), 1433–1438. doi:10.1073/pnas.1012475108

Ren, X. Y., Yang, J., Sun, R. M., Zhang, L. J., Zhao, L. F., Li, B. Z., et al. (2016). Viral IL-10 Down-Regulates the "MHC-I Antigen Processing Operon" through the NF-Kb Signaling Pathway in Nasopharyngeal Carcinoma Cells. Cytotechnology 68 (6), 2625–2636. doi:10.1007/s10637-016-9987-9

Reynert, N. L., Kless, K., Korn, S. H., Vos, N., Guala, A. S., Wouters, E. F., et al. (2004). Nitric Oxide Represses Inhibitory kappaB Kinase through S-Nitrosylation. Proc. Natl. Acad. Sci. U. S. A. 101 (24), 8945–8950. doi:10.1073/pnas.0400588101

Richardson, B. G., Jain, A. D., Speltz, T. E., and Moore, T. W. (2015). Non-electrophilic Modulators of the Canonical Keap1/Nrf2 Pathway. Bioorg Med. Chem. Lett. 25 (11), 2261–2268. doi:10.1016/j.bmcl.2015.04.019

Robinson, M. F., Damjanov, N., Stamenkovic, B., Radunovic, G., Kitvitz, A., Cox, L., et al. (2020). Efficacy and Safety of PF-6665160 (Ritlecitinib), a Novel JAK3/TEC Inhibitor, in Patients with Moderate-To-Severe Rheumatoid Arthritis and an Inadequate Response to Methotrexate. Arthritis Rheumatol. 72 (10), 1621–1631. doi:10.1002/art.41316

Rosenkrantz, S., Feldman, J., McLaughlin, V., Rischar, F., White, J., Ephremi, R., et al. (2017). The ARROW Study: A Phase 2, Prospective, Randomized, Double-Blind, Placebo-Controlled Study of Selonristib in Subjects with Pulmonary Arterial Hypertension. Eur. Respir. J. 50 (Suppl. 61), OA1983. doi:10.1183/13993003.congress-2017.oa1983

Ross, Y., and Magee, M. (2021). Use of Upadacitinib in the Treatment of Psoriatic Arthritis. Immunotherapy 13 (18), 1549–1554. doi:10.2217/imt-2021-0130

Rynhoud, H., Gibson, J. S., Meier, E., and Soares Magalhães, R. J. (2021). The Association between the Use of Oclacinib and Antibacterial Therapy in Dogs with Allergic Dermatitis: A Retrospective Case-Control Study. Front. Vet. Sci. 8, 631443. doi:10.3389/fvets.2021.631443

Sachse, F., Becker, K., Basel, T. J., Weiss, D., and Rudack, C. (2011). IKK-2 Inhibitor TPCA-1 Represses Nasal Epithelial Inflammation In Vitro. Rhinoology 49, 168–173. doi:10.4193/Rhino10.099

Saeed, M. E. M., Krishna, S., Greten, H. J., Kremsner, P. G., and Effert, T. (2016). Antischistosomal Activity of Artemisinin Derivatives In Vivo and in Patients. Pharmaco col. Res. 110, 216–226. doi:10.1016/j.phrs.2016.02.017

Sampaio, O. M., Vieira, L. C. C., Bellete, B. S., King-Diaz, B., Lotina-Hennsen, B., Veiga, T. A. M., et al. (2018). Evaluation of Alkaloids Isolated from Ruta graveolens as Photosynthesis Inhibitors. Molecules 23 (10), 269. doi:10.3390/molecules23010269

Sanda, T., Asamitsu, K., Ogura, H., Iida, S., Usutomiya, A., Ueda, R., et al. (2006). Induction of Cell Death in Adult T-Cell Leukemia Cells by a Novel IkappaB Kinase Inhibitor. Leukemia 20, 590–598. doi:10.1038/sj.leu.2404129

Sanda, T., Iida, S., Ozumi, H., Asamitsu, K., Murata, T., Bacon, K. B., et al. (2005). Growth Inhibition of Multiple Myeloma Cells by a Novel IkappaB Kinase Inhibitor. Clin. Cancer Res. 11, 1974–1982. doi:10.1158/1078-0432.CCR-04-1936

Santarpia, L., Lippman, S. M., and El-Naggar, A. K. (2012). Targeting the MAPK-RAS-RAF Signaling Pathway in Cancer Therapy. Expert Opin. Ther. Targets 16 (1), 103–119. doi:10.1517/14728222.2011.645805

Sarker, D., Dawson, N. A., Aparicio, A. M., Dorff, T. B., Puntuck, A. J., Vaishampayan, U. N., et al. (2021). A Phase I, Open-Label, Dose-Finding Study of GS263677, a PI3Kdelta Inhibitor, Administered with Enzalutamide in Patients with Metastatic Castration-Resistant Prostate Cancer. Clin. Cancer Res. 27, 5248–5257. doi:10.1158/1078-0432.CCR-21-1115
Zhang, C. A., and Lomonte, A. B. (2012). Tofacitinib for the Treatment of Rheumatoid Arthritis. Expert Rev. Clin. Immunol. 8 (4), 319–331. doi:10.1586/eri.12.19

Zhang, F., Qian, L., Flood, P. M., Shi, J. S., Hong, J. S., and Gao, H. M. (2010). Inhibition of IkappaB Kinase-Beta Protects Dopamine Neurons against Lipopolysaccharide-Induced Neurotoxicity. J. Pharmacol. Exp. Ther. 333, 822–833. doi:10.1124/jpet.110.165829

Zhang, H., Niu, X., and Qian, Z. (2015). The C-Jun N-Terminal Kinase Inhibitor SP600125 Inhibits Human Cytomegalovirus Replication. J. Med. Virol. 87, 2135–2144. doi:10.1002/jmv.24286

Zhao, Y., Spigolon, G., and Bonny, C. (2012). The JNK Inhibitor D-JNKI-1 Blocks Apoptotic JNK Signaling in Brain Mitochondria. Mol. Cell. Neurosci. 49, 300–310. doi:10.1016/j.mcn.2011.12.005

Zhong, Y., Zhang, F., Sun, Z., Zhou, W., Li, Z. Y., You, Q. D., et al. (2013). Drug Resistance Associates with Activation of Nr2f in MCF-7/DOX Cells, and Wogonin Reverses it by Down-Regulating Nr2f2-Mediated Cellular Defense Response. Mol. Carcinog. 52 (10), 824–834. doi:10.1002/mc.21921

Zhu, K., Liu, X., Liu, C., Xu, Y., Fu, Y., Dong, W., et al. (2021). AKT Inhibitor AZD3563 Suppresses Stemness and Promotes Anti-cancer Activity of 3,3'-diindolylmethane in Human Breast Cancer Cells. Toxicol. Appl. Pharmacol. 429, 115700. doi:10.1016/j.taap.2021.115700

Zhu, P., Qian, J., Xu, Z., Meng, C., Zhu, W., Ran, F., et al. (2021). Overview of Piperlongumine Analogues and Their Therapeutic Potential. Eur. J. Med. Chem. 220, 113471. doi:10.1016/j.ejmech.2021.113471

Zhuang, S. (2013). Regulation of STAT Signaling by Acetylation. Cell. Signal. 25 (9), 1924–1931. doi:10.1016/j.cellsig.2013.05.007

Ziegelbauer, K., Gantner, F., Lukacs, N. W., Berlin, A., Fuchikami, K., Niki, T., et al. (2005). A Selective Novel Low-Molecular-Weight Inhibitor of IkkappaB Kinase-Beta (IKK-Beta) Prevents Pulmonary Inflammation and Shows Broad Anti-inflammatory Activity. Br. J. Pharmacol. 145, 178–192. doi:10.1038/sj.bjp.0706176

Zimmermann, G., Papke, B., Ismail, S., Vartak, N., Chandra, A., Hoffmann, M., et al. (2013). Small Molecule Inhibition of the KRAS-PDE5 Interaction Impairs Oncogenic KRAS Signalling. Nature 497 (7451), 638–642. doi:10.1038/nature12205

Zirlik, K., and Veelken, H. (2018). Idelalisib. Recent Results Cancer Res. 212, 243–264. doi:10.1007/978-3-19-91439-8_12

Zou, L. J., Xiang, Q. P., Xue, X. Q., Zhang, C., Li, C. C., Wang, C., et al. (2019). Y08197 Is a Novel and Selective CBP/EP300 Bromodomain Inhibitor for the Treatment of Prostate Cancer. Acta Pharmacol. Sin. 40 (11), 1436–1447. doi:10.1038/s41401-019-0237-5

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