Preclinical Advances in SHP2 Beyond Oncology: An In-Depth Systematic Review of Emerging Preclinical Evidence for SHP2 Treatment in Non-Cancer Applications: A Ten-Year Overview

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ABSTRACT

Aim/Background: The function of Src Homology 2-containing Phosphotyrosine Phosphatase (SHP2) in oncology has been established with elaborate systematic reviews. Similarly, researchers have identified its role in non-cancerous conditions such as idiopathic pulmonary fibrosis, acute lung injury, cardiac fibrosis, systemic sclerosis, osteoarthritis, systemic lupus erythematosus, etc., but systematic reviews are limited. Hence, this systematic review seeks to compile the existing preclinical literature on the impacts of SHP2 in non-cancer disease conditions.

Materials and Methods: This review adheres to the Preferred PRISMA (Reporting Items for Systematic Reviews and Meta-Analyses) guidelines. This search was made across 6 databases, such as Medline, PubMed, EMBASE, Cochrane Collaboration Library, PubMed Central, and Google libraries, for the original research publications examining the preclinical impact of SHP2 on non-cancer diseases.

Results: A total of 76 articles were identified, and after eliminating unsuitable articles, 15 articles were included in the qualitative synthesis. They were sourced from four different countries, with 10 articles (66.6%) attributed to researchers from China, followed by 2 articles (13.3%) each from the United States and South Korea, and 1 article (6.7%) from France. Among the 15 articles, 11 (73.3%) concentrated on diseases, while 4 (26.7%) examined the inhibitory effects of SHP2 and its expression in treatment strategies. Most studies utilized SHP099 as the SHP2 inhibitor, while only one study employed a small-molecule inhibitor targeting Y279C SHP2 (compound 99).

Conclusion: The present review emphasizes the potential of SHP2 as a therapeutic target for non-cancerous diseases, acting as both an agonist and antagonist depending on the specific deficiency or overexpression linked to the condition. The insights regarding SHP2 are encouraging, prompting this study to call for additional research, especially in the realm of clinical trials. This is particularly relevant for diseases such as idiopathic pulmonary fibrosis, where lung transplantation is the only available treatment, yet it frequently remains out of reach for many individuals due to prohibitive costs and uncertain accessibility.

Keywords: MEK pathway, Non-cancer diseases, SHP2, SHP099, Src homology 2-containing phosphotyrosine phosphatase.

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Introduction

Cellular mechanisms often result in modifications to cellular traits and functions due to molecular interactions, which can lead to a variety of disease conditions, such as cancer and cardiovascular diseases.[1] Therefore, gaining insight into these signaling pathways is essential for identifying viable drug targets. Oncogene addiction refers to the phenomenon whereby various proto-oncogenes within cells become irreversibly activated as oncogenes due to genetic alterations, including amplification, rearrangement, and mutations. The occurrence and distribution of genetic mutations or abnormalities in the Rat Sarcoma (RAS) gene exhibit variability, despite RAS being one of the most frequently mutated oncogenes linked to human cancers.[2-4] Approximately 86% of RAS mutations involve the Kirsten Rat Sarcoma 2 viral oncogene homolog (KRAS), which is

the most commonly mutated variant.[5,6] Recent research has revealed that the KRASG12C inhibitor JDQ443 exhibits enhanced preclinical anticancer efficacy when used in conjunction with the Src Homology 2-containing Phosphotyrosine Phosphatase (SHP2) inhibitor TNO155.[7] In addition, the regulation of progenitor cell growth, tissue inflammation, cellular chemotaxis, and cellular proliferation is significantly influenced by SHP2. It is also well established that SHP2 directly contributes to the survival of cellular governance through processes associated with oxidative stress.[8] As a result, targeting SHP2's interactions with diverse proteins via its SH2 domains offers an intriguing possibility for a wide range of disease-specific pharmaceutical therapies.

In their 2004 study, Azuma *et al*.[9] demonstrated the binding affinity of two principal subtypes of CagA from Helicobacter pylori, specifically the East Asian and Western types, to SHP2. Simultaneously, increased expression of SHP2 was observed in aortic vascular smooth muscle cells[10], contributing to aortic atherosclerosis by promoting cell growth. In contrast, Tao *et al*. (2014)[11] identified a role for SHP2 in alveolar macrophages, where it is necessary to inhibit the progression of M2-associated pulmonary fibrosis. Additionally, other researchers have reported decreased levels of SHP2 in individuals with Idiopathic Pulmonary Fibrosis (IPF) [12] and acute lung injury. Inhibition of SHP2 has shown promising improvements in conditions such as cardiac fibrosis[13], systemic sclerosis[14], Osteoarthritis (OA) [15], and Systemic Lupus Erythematosus (SLE) [16]. It is evident that SHP2 can play varying roles in treating different non-cancer conditions depending on its molecular pathway. Consequently, this systematic review aims to consolidate the existing literature on the *in vitro* and preclinical effects of SHP2 in non-cancer conditions, as well as to delineate the molecular pathways and mechanisms involved in SHP2 regulation.

MATERIALS AND METHODS

The present systematic review complied with the Preferred PRISMA (Reporting Items for Systematic Reviews and Meta-Analyses) guidelines.[17] The research questions were formulated using the PICO framework.[18] Population-cell lines derived from non-cancerous conditions; Intervention-treatment with SHP2; Comparison-untreated SHP2; and Outcomes-analysis of the response of non-cancerous cells to SHP2 treatment through *in vitro* functional assays. The aims of the study included: "Does SHP2 have the potential to act as a non-anticancer agent?" "Are there any biological processes mediated by SHP2 in non-malignant cell lines?" and "Does SHP2 demonstrate modulation effects and function as a noteworthy non-antineoplastic agent?"

Search Strategy

We searched Medline, PubMed, EMBASE, the Cochrane Collaboration Library, Pubmed Central, and Google libraries for the original research publications examining the *in vitro* impact of SHP2 on non-cancer cells. A literature search was conducted to retrieve items published between November 2014 and November 2024. The search method included the following keywords: ("non-cancer cell" [MeSH] AND "*in vitro* studies" [MeSH] AND "SHP2" [MeSH] AND "Src homology 2-containing phosphotyrosine phosphatase inhibitors" [MeSH] AND ("humans" [MeSH]).

Study Selection Including Inclusion and Exclusion Criteria

Two unbiased reviewers did a preliminary inspection according to headings and abstracts, classifying research as "ok," "no," or "probably" depending on eligibility requirements. The complete text reading was limited to investigations labeled as "ok" or "probably." The eligibility criteria were followed in both steps. Articles evaluating the effects of SHP2 therapy on the biological behavior of non-malignant tumor cells were chosen for this systematic review.

The search for information was conducted with no time or language constraints. This systematic review omitted four categories of articles: (i) studies using only cancer cells; (ii) clinical studies concerned with cancer; (iii) studies that did not evaluate SHP2; and (iv) investigations that employed solely *in silico* analysis or bioinformatics. Two anonymous reviewers chose the articles separately, and any disagreements were addressed by consent.

RESULTS

Research Description:

A total of 76 articles were identified; following the removal of 11 duplicates, 65 articles were available for initial screening based on their titles and abstracts. Of these, 41 articles related to cancer research were subsequently excluded, resulting in 24 articles that proceeded to the next stage of evaluation. After a thorough review of the full texts, 9 articles were discarded, leaving 15 articles that were incorporated into the qualitative synthesis, as illustrated in Figure 1.

The studies selected for this review were published between 2014 and 2024 and were all authored in English. They originated from four different countries, with 10 articles (66.6%) attributed to Chinese researchers, followed by 2 articles (13.3%) each from American and Korean authors, and 1 article (6.7%) from France. Among the 15 articles, 11 papers (73.3%) focused on diseases, while 4 papers (26.7%) discussed the inhibitory effects of SHP2 and its expression in treatment strategies. Most studies utilized SHP099 as the SHP2 inhibitor, whereas only one study employed an Y279C SHP2 inhibitor which is small-molecule known as compound 99. Detailed information regarding the selected studies is presented in Table 1.

S. No	Author, Year of publication, Country	Disease/ Biological process	Preclinical model	Anti-SHP2 molecule	Effect	Pathway molecules	Outcome
1	Hsu MF et al.,2024, USA and China 19	Alcohol-associated liver disease (AALD)	Mouse (AALD model)-SHP2 gene disruption in vivo	SHP099	Ameliorated hepatic injury, inflammation (including intestine), stress and steatosis.	ERK pathway. (stress signalling)	SHP2 inhibition is a promising tool for AALD
2	Perrin et al., 2024, France 20	Congenital pseudarthrosis of the tibia (CPT)	Prss56-NF1 Schwann cells of knockout mice	Paracrine factors including TGF-β and induced fibrotic differentiation of wild-type skeletal SSPCs	Knock out SHP2 (SHP2 inhibition) prevented fibrosis non-union	MEK-SHP2 inhibition (Ras/Raf/MEK/ ERK)	Inhibition of both MEK and SHP2 might be promising avenue for CPT
3	Han et al., 2024, China 21	Chronic inflammation - Diabetic nephropathy (DN)	SHP2-knockout mice (Macrophage-specific) and SHP2fl/fl mice injected-STZ	SHP099	Failure to release cytokines that trigger phenotypic changes and fibrosis in kidney cells	Molecular pathway involving NF-κB and MAPK, Pathway MAPK-NF-κB-dependent inflammatory cytokine	SHP099 preserved kidneys in diabetes
4	Yang C et al., 2023, China 22	Systemic lupus erythematosus (SLE)	Pristane-induced lupus mice	SHP2 inhibitor treatment, (molecule not defined)	Reduction in hepatosplenomegaly and histological severity of the kidney	DCs, Th1, and Th17-differentiation of cells, reduction in production of inflammatory cytokines	SHP2 inhibition improved SLE pathogenesis
5	Chen et al., 2023, China 23	Aberrant decidualization	Murine models	SHP2 inhibitor RMC-4550 and shRNA-mediated SHP2	Decidualization deficiency	ERK phosphorylation, PR localization, IGFBP1, decidualization target genes	SHP2 is essential for decidualization process
6	Zhang et al.,2023, China 24	Bone development and remodelling	SHP2 conditional knockout mice	-	Affects bone development and remodelling though immune system, vasculature and nervous system	MAPK, IHH and PI3K/protein kinase B (AKT)	Lower expression of SHP2 is linked with bone development

7	Idrees et al., 2021, South Korea 25	Meiotic maturation	SHP2 was knocked down via RNA interference- bovine cumulus, human granulosa (COV434) cells	FSH, estradiol 2 treatment	FSH treatment-significantly enhanced cytoplasmic SHP2 localization, treatment with Estradiol 2 mediated localization of SHP2 into nucleus.	SHP2 in the cytoplasm regulates under expression of mRNAs of NPR2 and NPPC (ERα-transcribed) causing the arrest of oocyte during meiotic state (signaling - GPCR or RTKs)	Importance of cytoplasmic and nucleus SHP2 presence in oocyte somatic cells during meiotic resumption and maturation.
8	Wang et al., 2021, China 26	IVD (Intervertebral disc) degeneration (IDD)	Nucleus pulposus (NP) cells (in vitro and in vivo) in rats	SHP099 administration in rats via injectable thermosensitive hydrogels formulated with N-isopropyl acrylamide.	SHP2 highly expressed in degenerated IVDs, over expression NP cells- inhibits Sox9 (Sry-related HMG box-9) reduced collagen II, and aggrecan expression	Sox9	SHP2 inhibitors is promising therapeutic approach for IDD
0	Wang Q et al., 2021, China 27	Influenza A virus (IAV)	In vivo and in vitro	Pharmacological suppression, SHP2 silencing siRNA- IFN enhanced-dependent antiviral activity and reduced virion production.	Viral replication, concomitant with diminished immune function.	EGFR/ERK pathway	Better understanding of reason behind evasion of immune system and offers a novel drug attitude to infection by virus.
10	Tao T et al.,2021, China15	Osteoarthritis (OA)	Mice model	siRNA mediated knockdown of SHP2 or plasmid overexpression	Effectively delayed cartilage destruction and reduced osteophyte formation	Activated SHP2 -Wnt/β-catenin signaling - β-catenin. Inflammation caused by the induction of SHP2 mediated NF-κB and MAPK and pathways.	SHP2 inhibitor is a new and impending target of OA therapy
11	Kim et al., 2020, USA 28	Noonan syndrome with multiple lentigines (NSML).	Y279C SHP2 also known as compound 99	Compound 99	Uniquely inhibits Y279C SHP2 by irreversibly binding to the pathogenic cysteine residue in	-	SHP2 inhibition acts as foundational reference for the developme

					time-dependent, and substrate-independent, manner		nt of therapeutic agents targeting NSML
12	Yue et al.,2020, China 29	Temporal lobe epilepsy (TLE) (spontaneous recurrent seizures)	Pilocarpine-induced C57BL/6 mouse model	SHP099	Increased gliosis (reactive), IL-1β release, apoptosis of neurons. Reduced neurogenesis, albumin leak	-	SHP2 inhibition might be potential therapeutic approach for TLE
13	Cheng Y et al.,2018, China 30	Pulmonary artery hypertension (PAH)	Monocrotaline (MCT)-induced PAH rat model	Phps-1	Significant reduction in the proliferation and migration of human PASMCs induced by PDGF	Inactivation of Akt and Stat3 pathways	SHP2 inhibitors could be a viable target for therapeutic intervention
14	Park et al., 2017, Korea 31	Bacterial infections	Model not defined	Inhibition pharmacological/ SHP2 reduction in expression	TLR2 mediated transcription of IFN-β and activation of STAT1 pathway	GSK3β prevents phosphorylation of SHP2 and thereby transcription of IFN-β activation leading to TLR2 activation	Interaction between SHP2 and GSK3β in the regulation of TLR2-mediated IFN-β production in macrophages
15	Tzouvelekis A et al., 2017, USA 12	Idiopathic pulmonary fibrosis (IPF).	Model of bleomycin induced fibrosis lung of SHP2 with administration of lentivirus as well through transgenic mice	Molecule not defined	SHP2 expression reduction or activity – trigger-differentiation fibroblasts-myofibroblasts	Tyrosine kinases and serine/threonine kinases	SHP2 inhibitors acts as a therapeutics approach for IPF

Table 1. :
Role of SHP2 documented in the non-cancer diseases. Among the 15 included studies, the majority (n = 11, 73.3%) demonstrated a favourable therapeutic impact of SHP2 inhibition in mitigating disease pathology, particularly in models of fibrosis (e.g., idiopathic pulmonary fibrosis, cardiac fibrosis), autoimmune conditions (e.g., systemic lupus erythematosus, diabetic nephropathy), and musculoskeletal disorders (e.g., osteoarthritis, congenital pseudarthrosis of the tibia). SHP099 emerged as the most frequently utilized inhibitor, consistently reducing inflammatory signalling pathways such as MAPK, ERK, and JAK/STAT, as well as limiting cellular proliferation and fibrosis-related alterations. Two studies highlighted the agonistic roles of SHP2 in facilitating essential physiological functions, including oocyte maturation and decidualization, underscoring its dual regulatory role depending on biological context. Additionally, one study specifically targeted a disease-

associated SHP2 mutant (Y279C), marking progress in the development of mutation-specific pharmacological inhibitors. Overall, SHP2 acts as a context-dependent molecular modulator, with preclinical evidence largely supporting its potential as a promising therapeutic target in various non-cancer disease models.

DISCUSSION

Src Homology 2-containing Phosphotyrosine Phosphatase (SHP2) is increasingly recognized as a central player in diverse intracellular signalling networks. It modulates Receptor Tyrosine Kinase (RTK) cascades, including RAS-MAPK, PI3K-AKT, Hippo (SWH), and JAK/STAT pathways. Structurally, SHP2 comprises two SH2 domains (N-SH2 and C-SH2) that mediate binding to phosphorylated targets, and a PTP domain responsible for its enzymatic function. Activation occurs upon conformational changes induced by external stimuli, relieving auto-inhibition maintained through interaction between the PTP and N-SH2 domains. The conserved cysteine residue Cys459 and phosphorylation at Tyr542/Tyr580 are crucial for modulating SHP2 activity. These structural features have guided the development of SHP2 inhibitors that stabilize its inactive conformation (Figures 2A and 2b).

Over the last decade, growing preclinical evidence has highlighted SHP2's therapeutic relevance in a variety of non-cancerous diseases. Among these, liver injury, fibrosis, inflammation, immune dysregulation, and skeletal remodelling have emerged as key domains of interest.

For instance, in Alcohol-Associated Liver Disease (AALD), a condition for which no targeted pharmacotherapies currently exist, SHP2 inhibition using SHP099 demonstrated a protective effect. Hsu MF *et al*., (2024) reported significant reductions in hepatic inflammation, steatosis, and oxidative stress. Furthermore, SHP2 suppression also alleviated intestinal damage, preserved tight junction proteins, and reduced ERK pathway activation-underscoring its systemic protective effect in ethanol-induced injury models.[19]

Similarly, in Congenital Pseudarthrosis of the Tibia (CPT), a fibrotic bone disorder commonly associated with Neurofibromatosis type 1 (NF1), dual inhibition of SHP2 and MEK reversed fibrotic changes and resolved non-union lesions in a knockout mouse model. The findings by Perrin *et al*., (2024) highlight the role of SHP2 in TGF-β-mediated fibrotic differentiation of Schwann and skeletal progenitor cells, suggesting its inhibition as a promising antifibrotic strategy.[20]

In the context of chronic metabolic inflammation, Han *et al*., (2024) explored SHP2's role in diabetic nephropathy (DN). SHP2-deficient macrophages exhibited reduced expression of proinflammatory cytokines and fibrosis markers, preserving renal architecture in STZ-induced diabetic mice. Their transcriptomic analysis revealed downregulation of MAPK and NF-κB pathways, indicating a mechanistic basis for SHP2's involvement in renal inflammation.[21]

Autoimmune disease models also shed light on SHP2's complex immunoregulatory function. In systemic lupus erythematosus (SLE), Yang C *et al*., (2023) observed that SHP2 inhibition reduced hepatosplenomegaly, improved kidney histology, and decreased Th1/Th17 cell populations. The intervention also suppressed key inflammatory cytokines and pathogenic autoantibodies, confirming SHP2's involvement in the immunopathogenesis of lupus.[22]

Interestingly, SHP2 also appears to support essential physiological processes. Chen *et al*., (2023) demonstrated that during murine decidualization, SHP2 expression was critical for proper ERK activation and nuclear localization of the progesterone receptor. Inhibition through RMC-4550 or shRNA led to decidualization failure and embryo resorption, establishing SHP2 as a positive regulator of pregnancy maintenance.[23]

In skeletal biology, SHP2 plays a critical role in bone development and remodelling by modulating the maturation and differentiation of chondrocytes and osteoblasts. Zhang *et al*., (2023) delineated its involvement in major signalling cascades-including MAPK, PI3K/AKT, and Indian Hedgehog (IHH)-which interface with immune, vascular, and neural components to maintain bone homeostasis.[24]

Complementing this, Idrees *et al*., (2021) reported dual localization of SHP2 in oocyte maturation. Cytoplasmic SHP2 was found to suppress transcription of NPPC and NPR2 mRNAs, while nuclear translocation via estradiol enhanced oocyte reactivation, indicating compartment-specific roles during meiotic progression.[25] In degenerative disc disease, SHP2 was found to impair matrix integrity. Wang *et al*., (2021) showed that SHP099 delivery via thermosensitive hydrogel protected nucleus pulposus (NP) cells by preserving Sox9 and extracellular matrix proteins like collagen II and aggrecan-suggesting a therapeutic role in Intervertebral Disc Degeneration (IDD).[26]

Viral pathogenesis studies provide further evidence of SHP2's broader immune functions. In influenza A virus (IAV) infection, Wang Q *et al*., (2021) demonstrated that SHP2 supports EGFR/ERK-mediated viral replication while dampening IFN responses. Pharmacological inhibition or siRNA-mediated silencing of SHP2 restored interferon production and limited viral spread, reinforcing its role in innate immune evasion.[27] In inflammatory joint disorders

such as osteoarthritis (OA), Tao T *et al*., (2021) found that SHP2 enhanced catabolic and inflammatory responses via the Wnt/β-catenin, NF-κB, and MAPK pathways. SHP2 knockdown in chondrocytes reduced MMP expression and preserved matrix proteins, positioning SHP2 as a viable target for OA therapy.[15]

In the genetic disorder Noonan Syndrome with Multiple Lentigines (NSML), Kim *et al*., (2020) identified Compound 99, a small molecule that selectively binds and inhibits the pathogenic Y279C mutant of SHP2. Notably, this compound had minimal off-target effects on wild-type SHP2, illustrating the feasibility of developing mutant-specific therapies.[28] Neurological conditions also feature SHP2-mediated pathophysiology. Yue *et al*. (2020) investigated its role in temporal lobe epilepsy (TLE), revealing that SHP2 inhibition via SHP099 led to increased neuronal loss, reactive gliosis, and impaired neurogenesis-suggesting a neuromodulatory role for SHP2, with context-dependent outcomes.[29]

In pulmonary arterial hypertension (PAH), Cheng Y *et al*., (2018) showed that SHP2 inhibition by PHPS-1 reduced vascular remodelling, smooth muscle proliferation, and right ventricular hypertrophy in monocrotaline-induced rats. These effects were linked to downregulation of the Akt and Stat3 pathways, emphasizing SHP2's role in pulmonary vascular disease.[30] SHP2 also functions as a negative regulator in TLR2-driven innate immune responses. Park *et al*., (2017) demonstrated that SHP2 suppressed IFN-β production via interactions with GSK3β and transcription factors IRF1 and IRF8. This mechanism dampens STAT1 activation and inflammatory responses, potentially impacting host-pathogen dynamics.[31]

Lastly, in idiopathic pulmonary fibrosis (IPF), a progressive fibrotic lung disease with limited treatment options, Tzouvelekis A *et al*. (2017) reported that SHP2 was downregulated in fibroblasts of IPF patients. Its overexpression reduced fibroblast-to-myofibroblast transition and collagen deposition, while gain-of-function mutants or lentiviral SHP2 delivery conferred protection in murine models. These findings point to a protective, anti-fibrotic role for SHP2 in pulmonary remodeling.[12]

Taken together, the compiled evidence underscores the multifaceted roles of SHP2 across physiological and pathological settings. Whether acting as a driver of inflammation and fibrosis or as a crucial mediator of normal reproductive and developmental functions, SHP2 represents a context-dependent molecular modulator. Its therapeutic targeting must be disease-specific-leveraging inhibition in overactivation models and restoration in deficiency states. These findings pave the way for translational research, including biomarker-driven clinical trials in high-burden non-cancer diseases.

CONCLUSION

The current review highlights the potential of SHP2 as a target for non-cancerous diseases, functioning as both an agonist and antagonist based on the specific deficiency or overexpression associated with the disease. The findings related to SHP2 are promising, leading this study to advocate for further research, particularly in the context of clinical trials. This is especially pertinent for conditions like IPF, where lung transplantation remains the sole treatment option yet is often inaccessible to the general population due to high costs and uncertain availability.

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None

CONFLICT OF INTEREST

The authors declare that there is no conflict of interest.

ABBREVIATIONS

RAS: Rat Sarcoma; **KRAS:** Kirsten Rat Sarcoma 2 viral oncogene homolog; **SHP2:** Src Homology 2-containing Phosphotyrosine Phosphatase; **IPF:** Idiopathic Pulmonary Fibrosis; **PRISMA:** Reporting Items for Systematic Reviews and Meta-Analyses; **PICO:** Patient/Population, Intervention, Comparison and Outcomes; **RTK:** Receptor Tyrosine Kinase; **PI3K:** Phosphatidylinositol 3-Kinase; **SWH:** Salvador-Warts-Hippo; **JAK/STAT:** Janus Kinase/Signal Transducer and Activator of Transcription; **PTP:** Protein Tyrosine Phosphatase; **ALD:** Alcohol-Associated Liver Disease; **ERK:** Extracellular signal-Regulated Kinase; **ER:** Endoplasmic Reticulum; **CPT:** Congenital Pseudarthrosis of the Tibia; **NF1:** Neurofibromatosis type 1; **MAPK:** Mitogen-Activated Protein Kinase; **SSPCs:** Schwann cells and Skeletal stem/Progenitor Cells; **DN:** Diabetic Nephropathy; **SHP2-MKO:** SHP2-Knockout; **STZ:** Streptozotocin; **MPMs:** Mouse Peritoneal Macrophages; **RM:** Recurrent Miscarriage; **PR:** Progesterone Receptor; **IHH:** Indian Hedgehog; **FSH:** Follicle-Stimulating Hormone; **IVD:** Intervertebral Disc; **IDD:** Intervertebral Disc Degeneration; **NP:** Nucleus Pulposus; **Sox9:** Sry-related HMG box-9; **IAV:** Influenza A Virus; **EGFR:** Epidermal Growth Factor Receptor; **IFN:** Interferons; **ISGs:** Interferon-Stimulated Genes; **NSML:** Noonan Syndrome with Multiple Lentigines; **TLE:** Temporal Lobe Epilepsy; **PAH:** Pulmonary Arterial Hypertension; **MCT:** Monocrotaline; **PASMCs:** Pulmonary Artery Smooth Muscle Cells; **PDGF:** Platelet-Derived Growth Factor.

SUMMARY

This systematic review analyzed a total of 15 articles for a qualitative synthesis of the data. Researchers from

four different countries sourced these articles: 10 from China (66.6%), 2 from the United States and South Korea (13.3%), and 1 from France (6.7%). Among the 15 articles reviewed, 11 (73.3%) focused on diseases, while 4 (26.7%) investigated the inhibitory effects of SHP2 and its expression in treatment strategies. Most of the studies utilized SHP099 as the SHP2 inhibitor, while only one study used a small-molecule inhibitor targeting Y279C SHP2 (compound 99). This review highlights SHP2's potential as a therapeutic target for non-cancerous diseases, capable of acting as both an agonist and antagonist depending on the specific deficiency or overexpression associated with the condition. The insights gained regarding SHP2 are promising, leading this study to advocate for further research, particularly in the area of clinical trials. This is especially pertinent for diseases like idiopathic pulmonary fibrosis, where lung transplantation is often the only available treatment but frequently remains inaccessible to many individuals due to high costs and uncertain availability.

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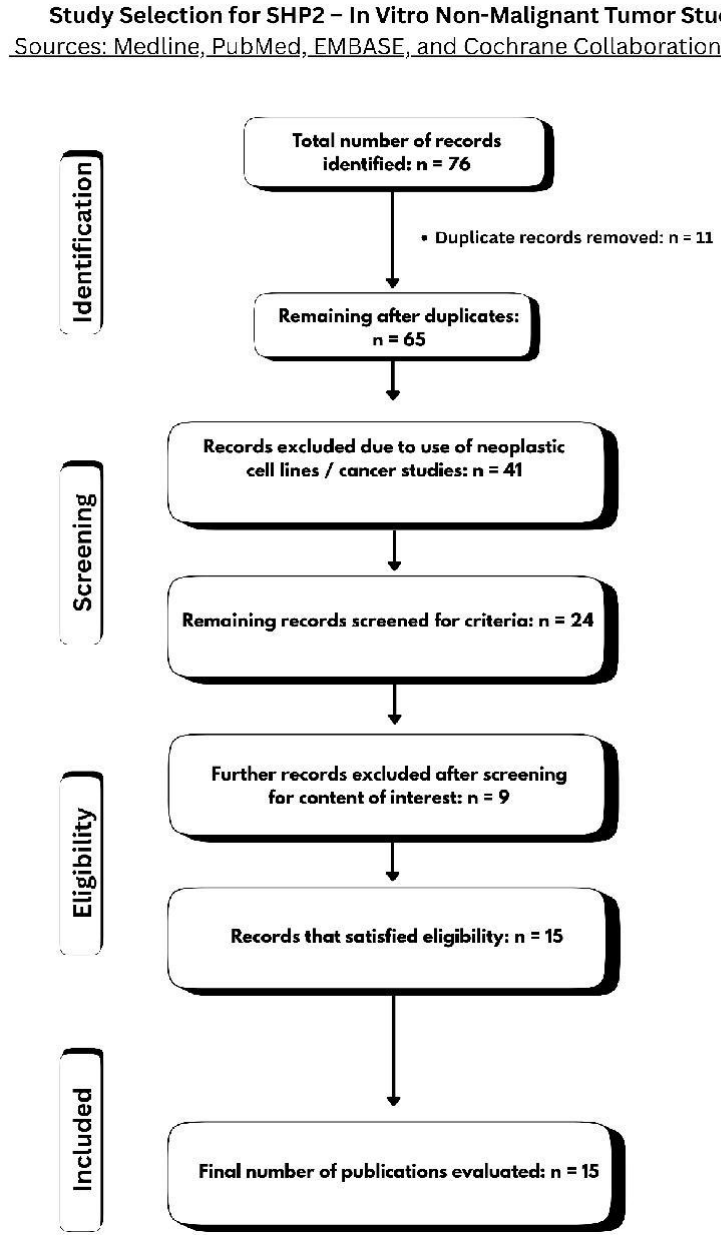

Figure 1:
Flow diagram of study selection using PRISMA.

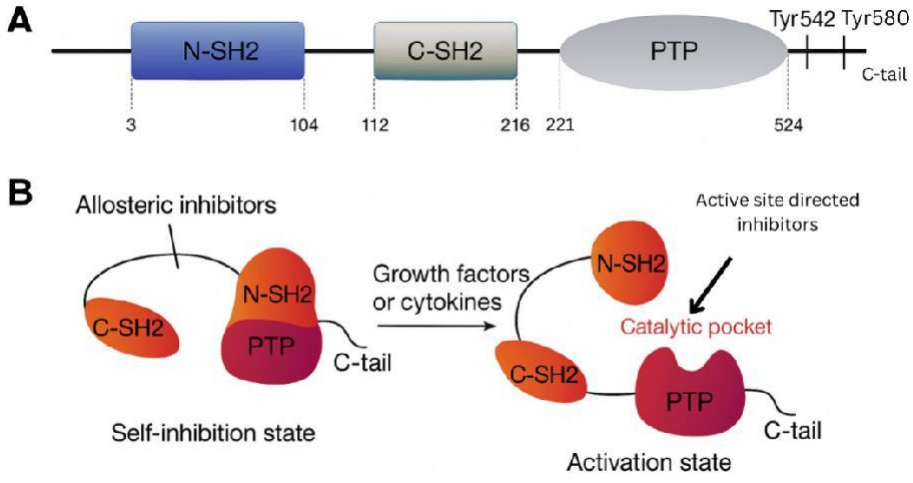

Figure 2:
(A) **SHP2 structure (B) Self-inhibition and activation state of SHP2 molecule.**