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Chapter

Importance of Protein Kinase and Its Inhibitor: A Review

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Abstract

Deregulation of a broad range of protein kinases has been linked to the development and growth of cancer cells. Protein kinases are intracellular enzymes that regulate cell growth and proliferation as well as the triggering and regulation of immune responses. Protein kinases are important therapeutic targets in cancer because of their critical role in signalling mechanisms that drive malignant cell characteristics. Intensive efforts in drug research have been made in this area over the last two decades. The current study delves into the catalytic domain of a protein kinase as well as information transfer from the cell's membrane to internal targets. It also discusses the function of protein kinases in signal transduction and their cellular signalling pathways. Furthermore, it specifically outlines a systematic method to hybrid therapies to solve the issue of protein kinase resistance. The therapeutic use of nitric oxide, as well as other targets such as Phosphoinositide 3-kinases (PI3K), Protein Kinase B (Akt), serine/threonine protein kinase (mTOR), p38 mitogen-activated protein kinases (p38 MAPK), vascular endothelial growth factor receptors (VEGFR), epidermal growth factor receptors (EGFR), and anaplastic lymphoma (ALK) etc., According to the review article, selective therapy has shown high effectiveness in the treatment of advanced cancer, with protein kinase inhibitors being a main focus of the therapy. As a result, the latest review summarized that, the current state of science with the aim of identifying a novel protein kinase inhibitor that may be utilized in the treatment of advanced cancers.

Keywords: Protein kinases, Signal Transduction, Cellular signalling pathways, NO and Anticancer

1. Introduction

The protein kinase enzyme family has been one of the most significant drug targets in the 21st century due to the dysregulation of protein kinase function in several diseases, including cancer. Protein kinases assume a crucial role in the intracellular transduction on account of their capability to phosphorylate plenty of proteins. In recent years, various protein kinase inhibitors have been recognized and are being utilized effectively in the clinical sector. In 2020, the FDA

approved the following medications for the treatment of the diseases listed: gastrointestinal stromal tumors), Capmatinib (non-small cell lung cancer), Pemigatinib (cholangiocarcinoma), Pralsetinib and Selpercatinib (non-small cell lung cancer, medullary thyroid cancer, and distinguished thyroid cancer), Selumetinib (neurofibromatosis type I), and Tucatinib (neurofibromatosis type I) (HER2-positive breast cancer). About every part of cellular activity is implicated in protein kinases [1]. It controls the metabolism, cell division and motion, movement, as well as immune and nervous system function and programmed cell death. The transfer of -phosphate from ATP to its protein substrates is catalyzed by protein kinase [2]. Protein kinase is a high-energy phosphate donor enzyme that donates a phosphate to other proteins. Phosphorylation is the process of converting one substance into another. In the reaction below, the substratum receives a group of phosphates and a phosphate group is donated by the high-energy ATP molecule. Trans-esterification results in a phosphorylated substrate; dephosphorylation is generated if the phosphoryphorylated substrate donates a phosphate group, and the phosphorylated substrate is grouped with ADP [3]. Protein kinases catalyze the following reaction:

$$MgATPl^- + Protein^-OH \rightarrow Protein^-O:PO32\_ + MgADP + H^+$$
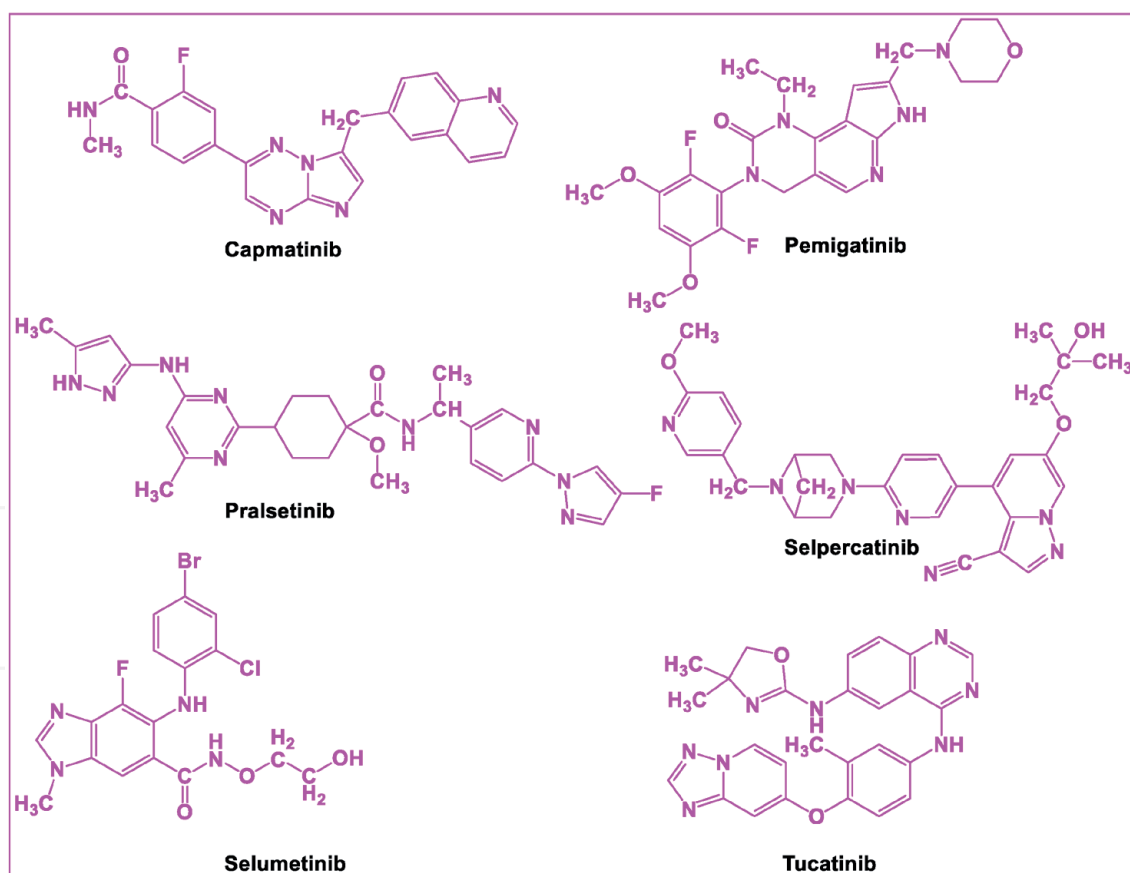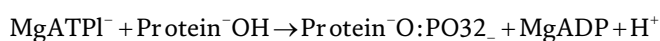
The human genome contains about 500 protein kinase genes, representing approximately 2% of all human genes [3]. Tyrosine kinases phosphorylate tyrosine hydroxyl groups in their targets, while serine/threonine kinases phosphorylate serine and threonine hydroxyl groups in their targets [4]. Protein kinases can be present in bacteria as well as plants. The majority of cellular pathways, especially those involved in signal transduction, are known to be regulated by kinases, and their actions can alter up to 30% of all human proteins. Protein

kinases are enzymes that phosphorylate serine, threonine, tyrosine, or histidine residues in proteins. Phosphorylation can affect the role of a protein in a number of ways. It has the ability to alter the function of a protein, stabilise or kill it, localise it in a particular cellular compartment, and start or stop its association with other proteins. Protein kinases make up the majority of kinases which have had a lot of criticism. Phosphatases are involved in the regulation of proteins and enzymes, as well as cell signalling. Aside from allosteric regulation, the potential to affect protein behaviour is tremendous [3], and there are many methods for covalently altering a protein. Allosteric regulation evolved to react to signals from inside the cell, while phosphorylation evolved to respond to signals from outside the cell, according to Edwin Krebs' Hopkins Memorial Lecture. The fact that eukaryotic cells phosphorylate proteins even more frequently than prokaryotic cells supports this theory, implying that the more complicated cell form has evolved to react to a broader spectrum of signals [5]. The chemical feature of a kinase is to covalently attach an ATP phosphate group to one of three amino acids with a free hydroxyl group. While most kinases bind to serine and threonine, some (dual-specificity kinases) often bind to serine and tyrosine [3]. Protein kinases use two types of interactions to identify their physiological substrates in cells: (i) the active protein kinase site recognises the consensus phosphorylation sequence in the protein substratum, and (ii) distal interactions between the kinase and the substratum are mediated by binding a docking motif spastically isolated from the phosphorylation site in the substratum to a substratum. Protein kinases use these interactions to identify their protein substrates with extreme precision. The identification of possible protein kinase physiological substrates should be aided by understanding the molecular basis for these interactions. Since protein phosphorylation is so important, researchers have spent a lot of time trying to figure out how protein kinase signal transduction mechanisms work. Dysregulation of protein kinases is seen in a wide range of illnesses, including cancer and inflammatory conditions.

2. Importance of protein kinase's

Protein kinases are intracellular enzymes that regulate cell growth and proliferation as well as immune response triggering and control. Protein kinases are phosphotransferases that binds phosphate to the side chains of serine, threonine, or tyrosine residues in cells to phosphorylate them. Kinases are needed in the first phase of intracellular immune cell signalling. Kinases, for instance, bind to the intracellular component of receptors on T and B lymphocytes' cell surfaces, and once these receptors are engaged with their extracellular ligands, they trigger intracellular signalling cascades within these cells. Phosphate (P) is transferred from ATP to a serine, threonine, or tyrosine residue in protein by protein kinases (**Figure 1**). Phosphorylation acts as a 'molecular shift,' enabling proteins to be triggered or deactivated directly. Protein phosphatases, on the other side, catalyze the elimination of the -phosphate from the target protein, which inhibits kinase function and reverses phosphorylation results [1, 3]. Serine (Ser or S), threonine (Thr or T), and tyrosine (Tyr or Y) residues account for more than one third of all protein phosphorylation events (O-phosphorylation) [3]. Just 1.8 per cent of tyrosine residues are phosphorylated, compared to 86.4 per cent of serine residues, 11.8 per cent of threonine residues, and 11.8 per cent of tyrosine residues [3, 4]. Tyrosine phosphorylation is peculiar among post-transitional modifications (PTM) in the EGFR band, including a tyrosine kinase domain. Histidine (His or H) and aspartate (Asp or D) metabolites may also be N-phosphorylated, but this process is less robust
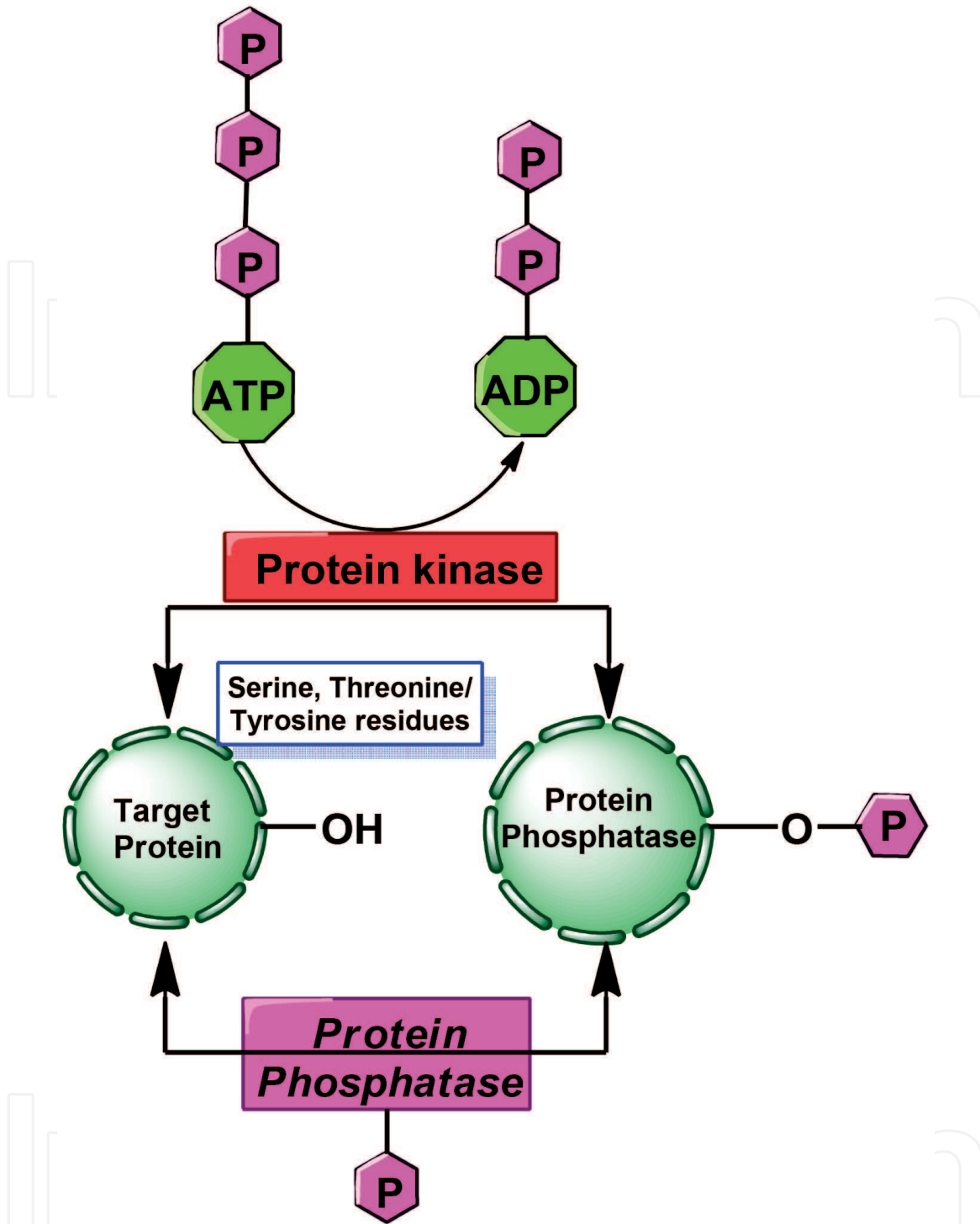
Figure 1.
Phosphorylation by protein kinase.

than other phosphorylation approaches. Since phosphorylation/dephosphoryla-
tion events mediated by different kinases and phosphatases trigger and deactivate
several enzymes and receptors, protein phosphorylation is a central regulating
mechanism in several cellular processes, including protein synthesis, cell division,
signal transduction, cell forming, development, and ageing. In addition, the human
genome contains 568 protein kinases and 156 protein phosphatases, both of which
control phosphorylation events and thus play a key role in biological processes such
as proliferation, differentiation, and apoptosis. Phosphorylation stimulates the p53
receptor, which stops gene replication, stops the cell cycle, starts DNA repair, and,
in certain instances, helps the cell die [2]. Chronic inactivation of the p53 protein

due to excess in the phosphorylation/dephosphorylation pathway will turn a cell cancerous. The 568 human protein kinases are classified based on the amino acid residues that they phosphorylate. The majority of kinases (serine/threonine kinases, or STKs) operate on both serine and threonine, while others (tyrosine kinases, or TKs) only work on one of the three amino acids (dual-specificity kinases; DSKs) [2]. STKs and TKs can be phosphorylated by the latter [6], with STKs accounting for about a quarter of all human protein kinases [2, 7]. STKs phosphorylate serine or threonine's OH group. DNA injury, as well as chemical signals like Ca2+/calmodulin, cyclic adenosine monophosphate/cyclic guanosine monophosphate (cAMP/cGMP), and diacylglycerol [8–16], trigger them. Protein kinase phosphorylation sets off a chain reaction that results in the phosphorylation of various amino acids [17]. Kinases may be programmed or deactivated in a variety of ways, including cis- or autophosphorylation, binding with activator or inhibitor proteins, or checking their localization in the cell with a substrate [3].

3. Catalytic domain of a protein kinase

The catalytic domain of a protein kinase is divided into two parts: N-terminal and C-terminal. A peptidic strand connects the two, forming an active site with a front pocket (catalytic residues) and a back pocket. A stored lysine residue and a residue "gatekeeper" control access to the back pocket. The catalytic domain is unavailable while activated since the propellers of the N- and C-terminal sub domains move inward. Non-catalytic domains of the kinases allow substrate attachment and signalling protein recruitment [3]. Kinases have gained in popularity in recent years, thanks to their functions in signal transduction and amplitude modulation, as well as their importance in signalling [18–20]. Many databases have been created to aid in the analysis of phospho-signalling networks [21, 22]. According to a review, protein kinases have been linked to over 400 diseases, either directly or indirectly. As a consequence, protein kinases are regarded as one of the most significant drug targets. Small molecular compounds that inhibit protein phosphorylation and thus resist activation can be used to target kinases. These small molecule inhibitors reduce kinase gene expression by disrupting ATP-kinase binding, intervening with kinase-protein interactions, and disrupting ATP-kinase binding. Protein kinase targets (SYK) include Janus kinase (JAK), mitogen-activated protein kinase (MAPK), and spleen tyrosine kinase [1–3].

4. Manifestation of signal transduction

The transmission of information from the cell's membrane to internal targets (within the cell) initiates a chain of molecular events that culminate in a biological response to the affector molecule (**Figure 2**). Advances in biochemical and molecular biological techniques have enabled the discovery of essential enzymes involved in the transduction phase, as well as the production of several natural and synthetic modulators of biological processes, over the last decade [5, 23]. Researchers have better understood molecular events in both natural and pathological settings because of these techniques. As new information regarding molecular interactions that regulate cellular responses has become accessible, the potential for designing and creating new drugs to cure cancer, central nervous system disorders (Alzheimer's disease), cardiovascular disorders (hypertension), skin disorders (inflammation), diabetes mellitus, and other chronic diseases has grown.
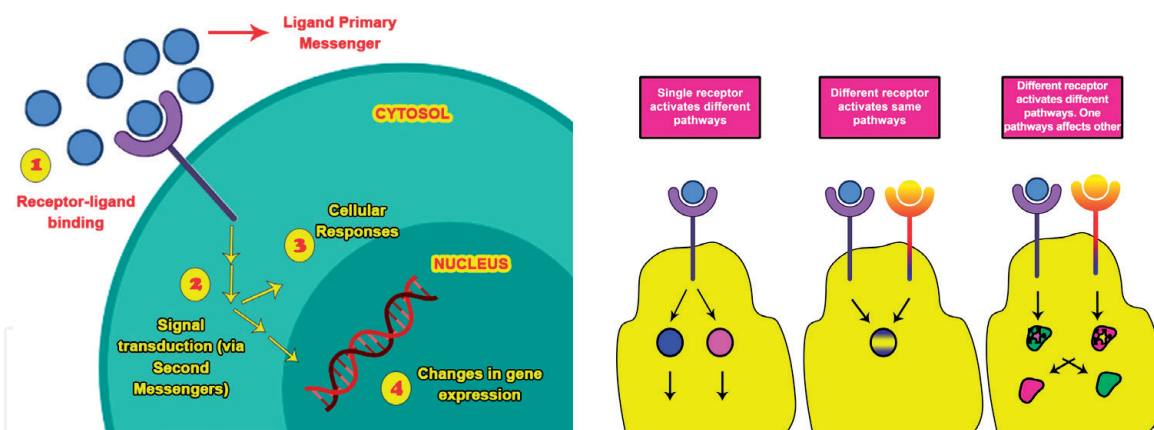
Figure 2.
The event of signal transduction.

5. Protein kinase's role in signal transduction

Second messengers such as cyclic AMP (adenosine monophosphate) and calcium are needed for the majority of isozymes to act [24, 25]. Kinases and phosphatases are known as "third messengers" because of this. Signal transduction is the process by which an extracellular primary signal is converted into an intracellular second messenger. In ligand-gated (ion channel) receptors, ion influx serves as a second messenger. G-protein-linked receptors can stimulate not only a second, but also a third and fourth messenger while they are activated. The ultimate endpoint could be the manipulation of gene transcription to generate messenger RNA (mRNA) and then mRNA translation to produce a protein specific to that gene. When a receptor attaches to a signalling molecule, it activates a signal transduction process. The four forms of messenger systems are as follows:

The first messengers are G-protein-linked messengers, kinases, and phosphatases, followed by phospho-calcium/cyclic AMP response element-binding (CREB) protein as the fourth messenger.

6. Protein kinase's role in cellular signalling pathways

Protein kinases play a number of roles in the body [26, 27]. Protein kinases are involved in variety of cellular signalling pathways **Figure 3** (phosphorylation). Protein kinases have different physiological functions in various systems, such as the cardiovascular system [27]. Troponin is triggered when PKA is activated, increasing the binding of excitation contractions. It also increases the contractility of the heart muscle. PKC activation phosphorylates other proteins in smooth muscles, despite the fact that cytosolic Ca++ combines with calmodulin (CAM) to activate myosin light chain kinase, causing smooth muscle contraction [25, 28]. Protein kinase A causes an increase in membrane water permeability by increasing the rate of exocytosis of water-containing vesicles (WCVs) into the apical membrane and decreasing the rate of endocytosis of WCVs from the apical membrane in the kidneys. The mitogen-activated protein (MAP) kinase pathway is activated by angiotensin I receptors (At1) in the kidney, which promotes cell development, especially in vascular and cardiac cells. It raises proton changes, particularly C-fos and C-jun, which regulate the transcription of several genes involved in cell growth [23]. At1 activates Protein Kinase A, which causes phosphorylation of proteins involved in aldosterone synthesis, neurotransmission facilitation, CNS outcomes, and renal impact.
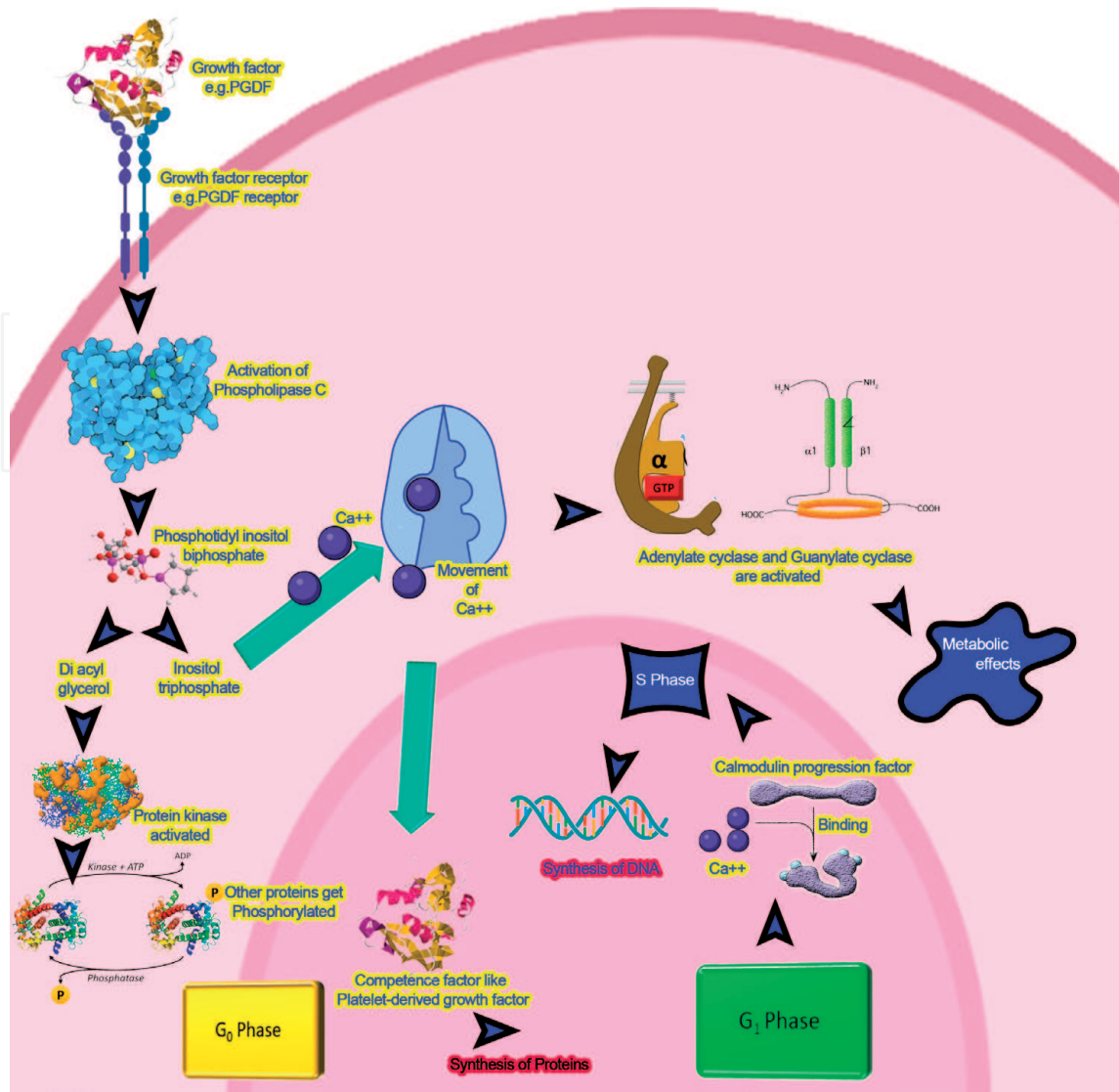
Figure 3.
The protein kinase sequence of signaling process.

7. A review of functions of protein kinases

Protein kinases assign a phosphate group from the ATP gamma location to specific amino acid residues in proteins and peptides. Protein phosphorylation is implicated in a variety of physiological processes, including glucose absorption, signalling, epigenetic modifications, and cell cycle progression. Diabetes, cardiovascular disease, Alzheimer's disease, and cancer, to name a few illnesses, have all been linked to phosphorylation deficiencies. Monitoring protein kinase activity is crucial for better understanding disease molecular mechanisms and determining whether or not a treatment is successful. Inhibiting pathological phosphorylation can aid in the treatment of these diseases as well [29]. The desire to solve the three-dimensional structures of many of these enzymes sparked interest in academia and the pharmaceutical industry due to these factors [30]. According to Steinberg SF, cyclin-dependent kinases (CDKs) are a form of serine/threonine kinase whose activity is mediated by cyclin, a protein regulatory subunit. Eukaryotic cell division and transcription are aided by CDKs. PKC is a serine/threonine kinase that regulates a variety of natural cellular responses and also plays a role in the pathogenesis of ischemia–reperfusion injury. The Abelson murine leukaemia virus (Abl) proto-oncogene is a non-receptor tyrosine kinase that is activated by both extrinsic ligands such as growth factor receptors and intrinsic

signals such as DNA damage and oxidative stress. c-Abl shuttles between the cytosolic and nuclear compartments, phosphorylates a variety of cellular substrates (including adaptor proteins, other kinases, cytoskeletal proteins, transcription factors, and chromatin modifiers), and controls signalling pathways implicated in actin polymerization and cytoskeletal remodelling, cell adhesion and motility, transcriptional regulation, and the DNA structure [30]. The mitogen-activated protein kinase 4 (MKK4) has been discovered to be a central regulator of liver regeneration, according to Klövekorn P et al., and could be a valuable drug goal for treating liver diseases by restoring the organ's intrinsic regenerative potential. According to Wüstefeld et al., MKK4 is a primary promotor for liver regeneration, with positive results on hepatocyte regeneration, robustness, fibrosis, and Fas-mediated apoptosis [31]. The primary intracellular energy sensor, according to Jovanovic-Tucovic et al., is AMP-activated protein kinase (AMPK), which triggers ATP-generating catabolic pathways while inhibiting ATP-requiring processes in response to the increase in the AMP/ATP ratio and/or oxidative stress. Depending on the form of stimuli and the intensity/length of AMPK activation, this serine/threonine kinase may be neuroprotective or neurotoxic, and its dysregulation has been attributed to neurodegenerative disorders including Parkinson's disease. Serine/threonine-protein kinase B/Akt is another crucial protein kinase for neuronal cell metabolism and survival. Phosphodiesterase 5A inhibitors, such as Sildenafil, have been shown to protect against ischemic injury by decreasing cardiac Na+/H+ exchanger (NHE1) activity, which is regulated by protein kinase G, as mentioned by Diaz RG et al. [32]. In 1954, Burnett and Kennedy discovered the Casein Kinase 2 (CK2) catalyst. It's a Ser/Thr protein kinase that's acidophilic and pleiotropic, and it's crucial for cell viability. When coupled with CK1, it acts as a catalyst, phosphorylating Casein protein in vitro (but not in vivo) [32]. The use of enacted AMP protein kinase as a therapeutic target for ischemia–reperfusion injury was identified by Rong Ding et al. [33].

The most popular drug targets include BCR-Abl, B-Raf, vascular endothelial growth factor receptors (VEGFR), epidermal growth factor receptors (EGFR), and ALK. The bulk of small molecule protein kinase antagonists adhere to the protein kinase domain and treat cancers such as myelofibrosis, polycythemiavera, persistent immune thrombocytopenia, rheumatoid arthritis, idiopathic pulmonary fibrosis, and glaucoma [34].

Human eukaryotic protein kinases (ePKs) have been divided into nine classes, according to Gaji et al. The following are examples of these: (1) the AGC group, which includes PKA, PKB (At1, At2, At3) PKG, and PKC; (2) the Ca^{2+}/calmodulin-dependent protein kinase (CAMK) group, which includes calcium/calmodulin-dependent protein kinases (CAMK) and mitogen activated protein kinase activating protein kinases (MAPKAPKs); (3) the casein kinase 1 (CK1) group, which has 12 members; (4) the CMGC group, which has 6161members including cyclin-dependent protein kinases (CDK), mitogen-activated protein kinases (MAPK), glycogen synthase kinase (GSK) and cyclin dependent kinase like (CDKL) families; (5) The STE group (related to yeast non-mating or sterile genes) has 47 members who are MAPK upstream regulators; (6) the tyrosine kinase (TK) group has 90 members, including 58 receptor protein kinases (RTKs) and 32 non-receptor tyrosine kinases; (7) the tyrosine kinase like (TKL) group has 43 members, and proteins in this family; (8) the receptor guanylylcyclase (RGC) group consists of five members; and (9) the 'other' group has 83 members. In addition, 40 kinases are known as atypical kinases, one of which is the mitochondrial pyruvate dehydrogenase kinase [35]. For types and classes of protein kinases refer **Tables 1** and **2**. AMP-activated protein kinase (AMPK) senses energy levels and controls metabolic processes to maintain homeostasis. The function of AMPK is influenced by the supply of nutrients such as carbohydrates, lipids, and amino acids. AMPK function is impaired by overnutrition,

Types	Examples	Functions
Serine/threonine-specific protein kinases	Calcium/calmodulin-dependent protein kinase II (CaMKII)	Phosphorylate serine or threonine's –OH (hydroxyl) functional group.
Tyrosine-specific protein kinases	Platelet derived growth factor (PDGF) receptor Epidermal growth factor (EGF) receptor1 Insulin growth factor (IGF1) receptor Stem cell factor (scf) receptor	Processes alzheimer's amyloid precursor protein, epithelial cell migration and carcinoma invasion, spermatogonia osmoregulation, and antiaging survival factor
Histidine-specific protein kinases	Histidine kinase	The histidine kinase family is structurally similar to the pyruvate dehydrogenase family of kinases in animals.
Mixed kinases	Muscle action potential kinase (MAPK)	Involved in the cascade of muscle action potential kinase

Table 1.
A summary the types of protein kinases based on amino acid residue.

Types	Functions			
Protein kinase A (PKA)	Acts as a catalyst, allowing intracellular proteins to be catalysed. Glycogen, sugar, and lipid metabolism are all regulated by this protein. Phosphorylate acetyl-CoA carboxylase and pyruvate dehydrogenase in adipocytes, myocytes, and hepatocytes, resulting in acetyl-CoA-lipogenesis. The dopamine signal is translated into cells in the nucleus acumens neurons.			
Protein kinase B (PKB)	Akt	Akt1	Akt2	Akt3
	Cell proliferation, apoptosis, transcription, and cell migration are all involved in glucose metabolism. Cell survival - both actively and indirectly facilitate growth factor-mediated cell survival. Glycogen synthesis is aided by metabolism. Angiogenesis is linked to tumour growth and angiogenesis.	Is implicated in: cellular survival pathways, by inhibiting apoptosis processes. skeletal muscle hypertrophy and general tissue growth. the transforming retrovirus as the oncogene	The insulin signalling pathway has been linked to this protein. Glucose transport induction is a term used to describe the process of causing glucose	It tends to be expressed primarily in the brain. The brains of mice lacking Akt 3 are weak.
Protein kinase C (PKC)	Phosphorylation of intracellular proteins is catalysed by this enzyme, which changes their activities. Controls cellular growth and differentiation.			

Table 2.
Summary of classes of protein kinases [34].

inflammation, and hypersecretion of certain anabolic hormones, such as insulin, which is exacerbated by food shortages and inhibited by obesity. According to Zhao and Saltiel, activating AMPK in the liver inhibits de novo lipogenesis, promoting fatty acid oxidation (β -oxidation). Furthermore, AMPK activation prevents hepatic steatosis by inhibiting the production of free fatty acids from adipose tissue (**Figure 4**) [36]. On the other side, Alghamdi et al. investigated the function of
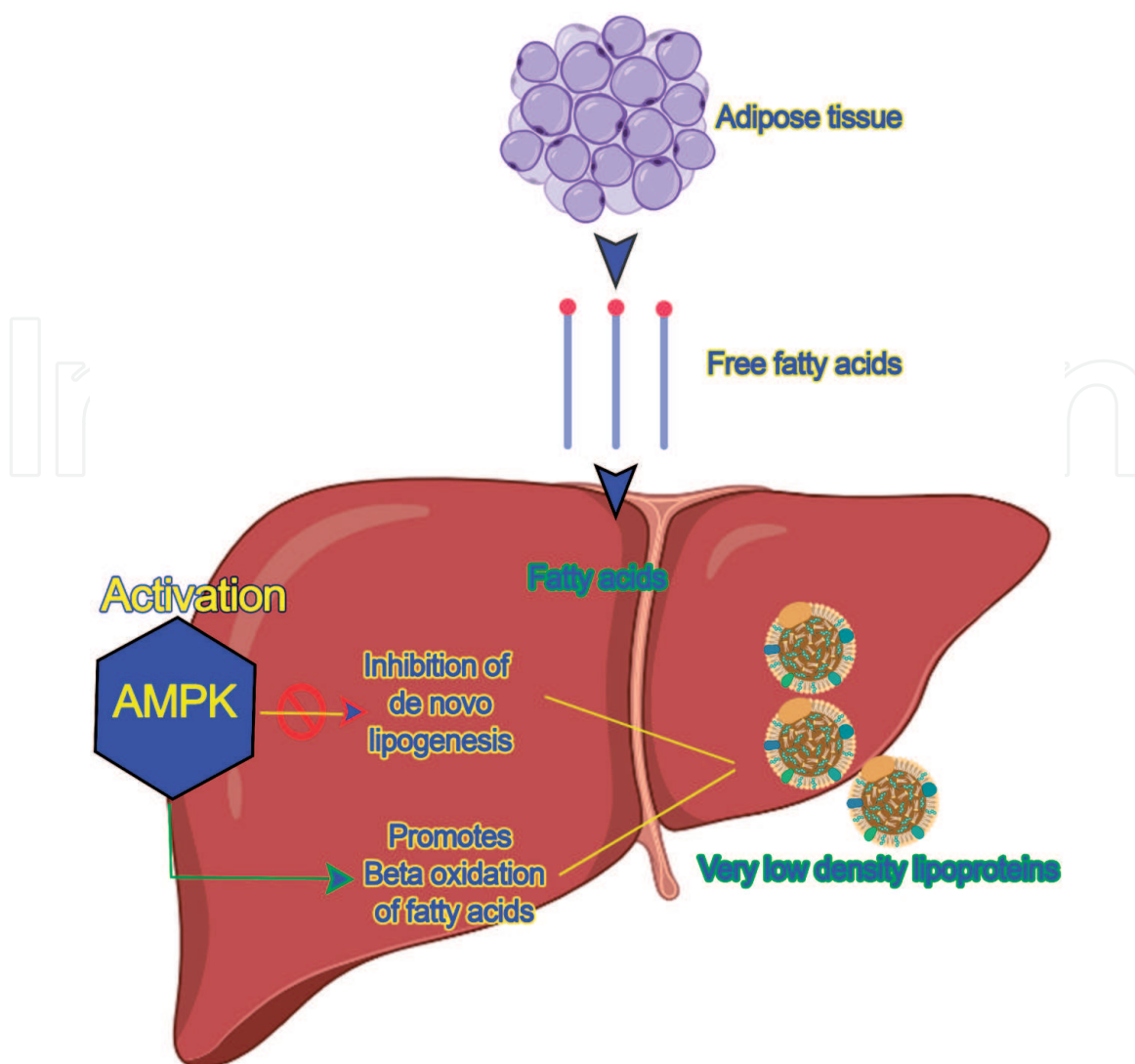
Figure 4.
Regulation of hepatic steatosis by AMPK.

AMPK in nutrient absorption by tissues, especially glucose and fatty acid uptake. Because of its impact on carbohydrate and lipid metabolism, rising FA oxidation and decreasing lipogenesis, AMPK activation has been proposed as a therapeutic goal for nutrient overload. In NAFLD/NASH (non-alcoholic fatty liver disease/non-alcoholic steatohepatitis), nutrient overload induces hepatic steatosis, which leads to fibrosis and liver injury. Hepatic steatosis is the accumulation of ectopic lipids in the liver and is closely linked to obesity, insulin resistance and type-2-diabetes.

De novolipogenesis (DNL) from carbohydrates or increased FA absorption and triglyceride synthesis cause lipid accumulation in the liver. Increased hepatic FA oxidation, on the other hand, reduces steatosis [37]. Li et al. results suggest that AMPK may be used as a clinical therapy for the treatment of cholestatic liver damage. The ability to evaluate the dose- and time-effects of AMPK activation in various models representing various stages of cholestatic liver injury is critical not just for determining the efficacy of AMPK as a targeted therapy for treating cholestatic liver injury, but also for providing crucial scientific proof for clinical practice and translational studies of existing AMPK inducers [38].

In recent pharmacological study, protein kinases have become one of the most widely researched therapeutic targets, especially in cancer and inflammation studies. For the treatment of cancer and inflammation, the US Food and Drug Administration has licenced 32 small-molecule protein kinase inhibitors. However, no medication successfully treats neuroinflammation and/or neurodegenerative conditions due to a lack

of protein kinase drug targets for CNS disorders. According to new findings, some protein kinases have recently been established as promising drug targets in the treatment of neuroinflammation and/or neurodegenerative diseases. Lee and Suk investigated a number of protein kinases that are increasingly being seen as potential therapies in microglia-mediated neuroinflammation (**Figure 5**). Because of their critical roles in neuronal toxicity, some of these kinases, such as LRRK2, MST1, and tyrosine kinases (c-Abl, Src, and Fyn), have been proposed as potential drug targets, while others were presented here as novel protein kinase drug candidates because of their critical roles in microglial activation [39]. Many neurodegenerative disorders, such as Parkinson's disease (PD), Alzheimer's disease (AD), and stroke, are due to microglia-mediated neuroinflammation. Microglia-mediated neuroinflammation has been compared to protein kinases such as leucine-rich repeat kinase 2 (LRRK2) and mammalian Ste20-like kinase 1 (MST1), Src family protein tyrosine kinases (SFKs), a cellular homolog of the Abelson murine leukaemia virus oncogene (c-Abl), and TAM family receptor tyros TLRs, TNFR, CD11b, and P2Y12 protein kinases are all known to play a role in microglial activation by relaying signals from different exogenous inducers through cell surface receptors. Parkinson's disease and Alzheimer's disease all have protein aggregates as a pathological function (a-synuclein [a-SYN] in PD and Ab peptides in AD). These protein aggregates bind to TLR, CD11b, and other microglial receptors, triggering a number of intracellular signalling pathways. They are activated as a consequence of neuronal death or other proliferation mechanisms. Bacterial lipopolysaccharide (LPS), adenosine diphosphate (ADP), tumour necrosis factor (TNF), and RNA
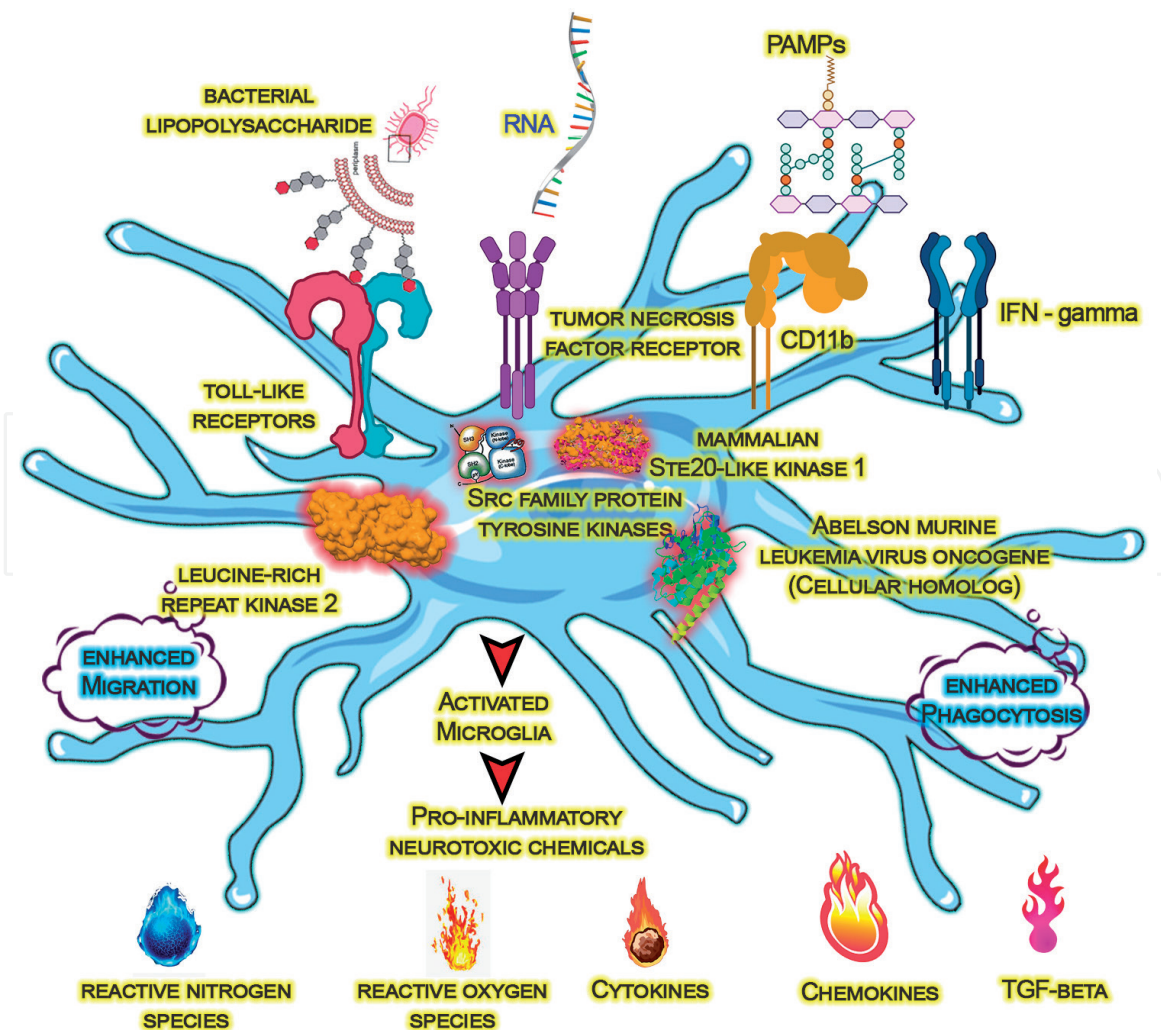

Figure 5.
Microglia-mediated neuroinflammation.

virus are among the other triggers that activate microglia through TLRs, P2Y12, and TNFR. TAM receptor tyrosine kinases including Axl and Mer are involved in several areas of microglia-mediated neuroinflammatory pathology in PD. As a consequence of their activation, activated microglia produce a broad variety of proinflammatory cytokines, chemokines, and reactive oxygen/nitrogen species (ROS/RNS). In response to stimuli and intracellular protein kinases, activated microglia increased migration and phagocytic action. Several studies have linked protein kinases to neuronal toxicity and microglial activation. In comparison to neurons, only a few protein kinases (PKs) have arisen as critical signalling components modulating microglial activation. Some kinases, such as Leucine-rich repeat kinase 2 (LRRK2), mammalian Ste20-like kinase 1 (MST1), tyrosine kinases, and mitogen-activated protein kinases (MAPKs), tend to be involved in both neuronal toxicity and microglial activation, while TAM receptor tyrosine kinases (RTKs) like Axl and Mer also recently emerged as new targeted therapies for inflammation caused by microglia [39].

According to Simon Diering et al., the modulation of the b1-adrenoreceptor (AR) signalling pathway regulates the contraction and relaxation of the heart by activating cAMP-dependent protein kinase (PKA) and subsequent cardiac protein phosphorylation. The key cardiac protein phosphatases, PP2A and PP1, prevent phosphorylation. Intra molecular disulfide formation in the catalytic subunits of
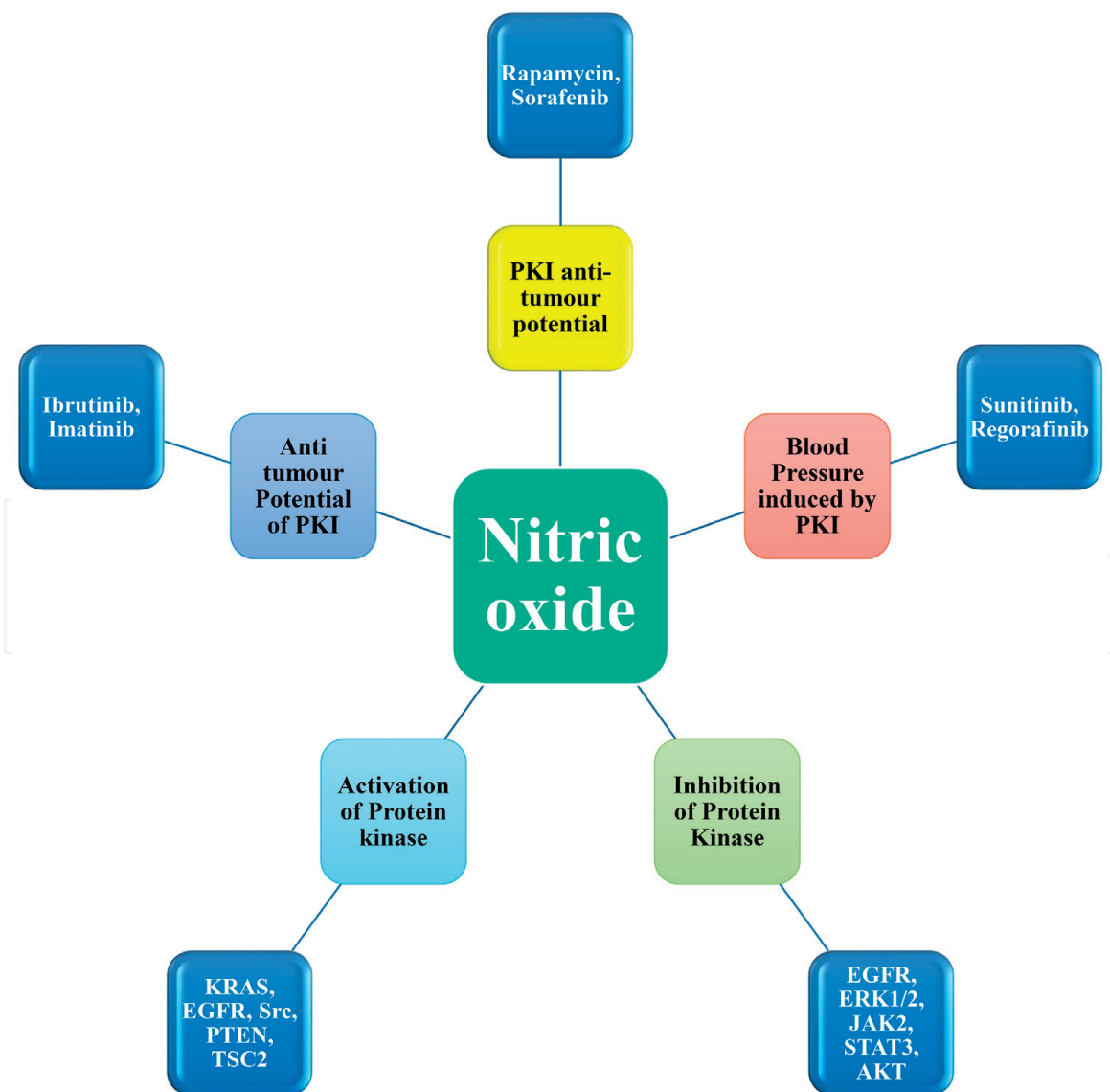

Figure 6.
Impact of NO on protein kinases and PKIs activities.

both kinases and phosphatases inhibits their function [40]. Hashemol hossein discovered that CK2 is involved in a number of phases in the biology of striated skeletal muscle, including myogenesis and homeostasis in adult muscle, as well as neuromuscular junctions, which connect muscle fibres and motor nerves. CK2 regulates protein import in myotube organelles, as well as the consistency and dignity of the postsynaptic machinery in neuromuscular junctions and the muscular cytoskeleton [40]. It's also becoming clear that CK2's function in processes that dynamically regulate the phosphoproteome of muscle cells is significant, and that it's likely to play a role in maintaining muscle homeostasis at the molecular level.

A wide range of protein kinase inhibitors (PKIs) have entered various stages of clinical development in the last two decades, with various properties and potential applications, such as different selectivity and modes of binding to kinases, and some have been licenced by the FDA. PKIs have therefore developed themselves as a significant class of cancer medicines, and their therapeutic ability continues to attract attention. In fact, studying kinase biology in relation to PKI development is an essential part of targeted therapies. The resistance of cancer cells to PKI therapies necessitates the development of new therapeutic options. As a result, new generation PKIs have been built and tested in the hopes of overcoming resistance. According to Ghione et al., NO may directly or indirectly regulate protein kinases involved in essential cancer signalling pathways, as seen with PKIs. The NO donor NTG has been studied in a growing number of clinical trials as an anticancer treatment when combined with radiotherapy or chemotherapy.

NO's ambivalent impact on PKI (encouraging or inhibiting PKI's anticancer potential) and the action of protein kinases are summarised (regulated at the transcriptional or the post-translational level by NO) **Figure 6** [41].

8. NO acts as a kinase activator

According to several reports, the intracellular production of NO by NOS is needed for the phosphorylation and subsequent activation of EGFR signalling pathways. Overexpression of iNOS in a number of tumours, including breast cancer, has been related to tumour development and angiogenesis. Indeed, high iNOS expression has been linked to EGFR phosphorylation, activation, and poor prognosis in various breast cancer subtypes.

9. NO acts as a kinase inhibitor

NO has been shown to have a detrimental regulatory impact on protein kinases in many experiments, which is compatible with its unclear role in cancer. By inhibiting the activity of many protein kinases, NO may inhibit pathways implicated in cancer cell proliferation and survival. For some of these protein kinases, selective protein kinase inhibitors (PKIs) are currently being investigated [41].

Mori et al. investigated whether the biguanide anti-hyperglycemic medication metformin dilates retinal blood vessels in rats. *In vivo*, photographs of the ocular fundus were taken with a high-resolution optical fundus camera, and the diameters of retinal blood vessels were determined. The pulse rate and systemic blood pressure were also constantly monitored. Metformin (0.01–0.3 mg/kg/min) raised the diameters of retinal blood vessels in a dose-dependent way. Metformin's retinal vasodilator effect was blocked by compounds, an AMPK inhibitor, and NG-nitro-L-arginine methyl ester, a nitric oxide (NO) synthase inhibitor. The AMPK activator

5-aminoimidazole-4-carboxamide-1-D-ribonucleoside (AICAR, 0.01–1 mg/kg/min) generated similar effects. The effects of metformin and AICAR on mean blood pressure and heart rate were not important. When NO synthase was inhibited, however, a significant presser reaction to AICAR was observed. These findings indicate that metformin activates AMPK, which dilates retinal blood vessels, and that NO plays a significant role in the retinal vasodilator reaction after AMPK activation (**Figure** 7). According to this report, the anti-diabetic medication metformin dilates retinal blood vessels by activating AMPK, which is the first pharmacological proof according to this report. Metformin inhibits inflammatory reactions and angiogenesis in the retina, in addition to lowering blood glucose levels. Aside from these benefits, the retinal vasodilator influence can help prevent or delay the development of diabetic retinopathy [42]. KN-93, a calmodulin-dependent protein kinase inhibitor, prevents neuronal cell viability in an *in vitro* Alzheimer's disease model, according to Yilmaz. Alzheimer's disease is the most prevalent form of dementia in people over the age of 65, and it is marked by memory loss that progresses over time. The neurofibrillary tangles formed by hyperphosphorylated tau and the senile plaques generated by the -amyloid peptide (A 1–4) are the key cardinal lesions consistent with Alzheimer's disease. CaMKII, a central enzyme in memory development, incorporates transient knowledge reflecting both past and current cellular behaviour into the complex essence of "continuous" calcium signalling. Although the alpha and beta isoforms of the CaMKII enzyme have been shown to play a role in memory development, the role of the gamma and delta isoforms is yet to be determined [43]. Researchers have continued to design and create new Rho kinase inhibitors throughout the decade after Fasudil was approved in Japan for the
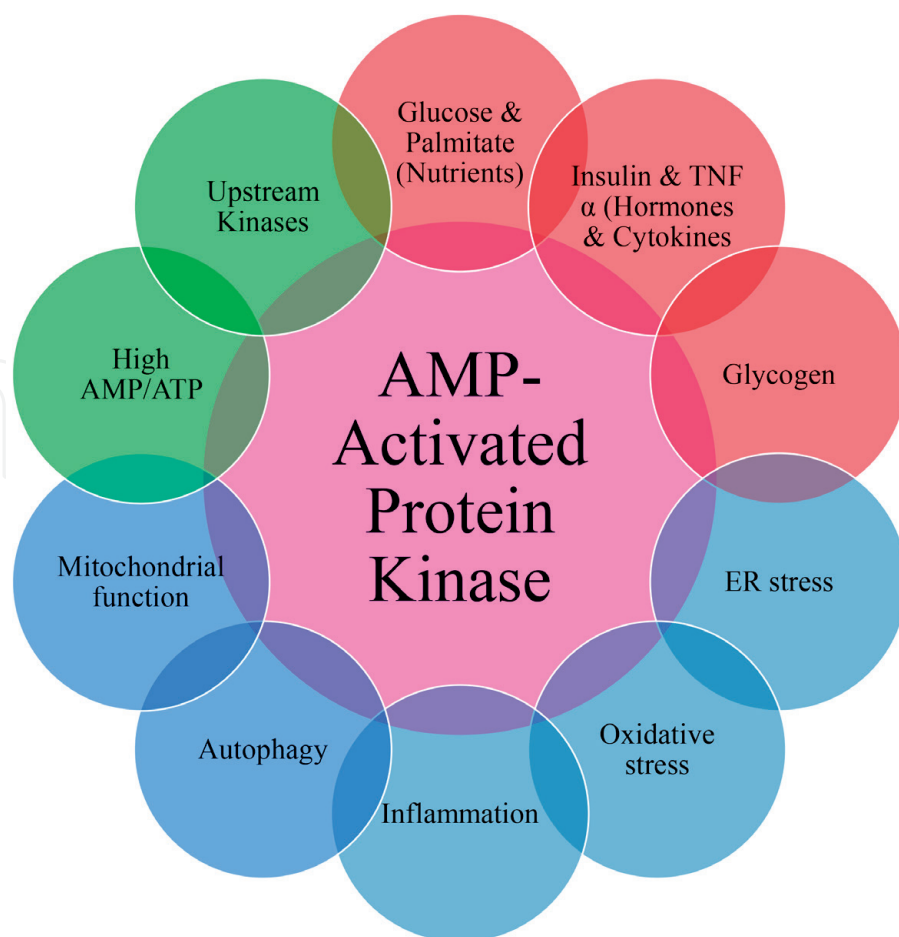

Figure 7.
*AMPK activated protein kinase.*

treatment and prevention of cerebral vasospasm and subarachnoid haemorrhage. Rho kinase inhibitors have been shown to be useful in the treatment of neurodegenerative conditions, coronary diseases, metabolic syndrome, and glaucoma. Both animal and human trials have supported the beneficial effect of Rho kinase inhibitors in the improvement of lung arterial relaxation and remodelling, suggesting that they may be useful in the treatment of pulmonary hypertension. According to Abedi et al., Rho kinase inhibitors have also been shown to be successful in the preventing and treating pulmonary fibrosis, with increasing confirmation that the Rho/ROCK signalling system is involved in actinomyosin contraction and actin filament assembly. Down regulation of the Rho/ROCK signalling system is aided by specific Rho kinase inhibitors. Rho induction has also been linked to other possible clinical uses. For example, statins' action on atherosclerosis has been linked to their Rho inhibitory effect, as has simvastatin's preventive role in chronic pulmonary hypertension. Inhibitions of RhoA activity and down regulation of Rho kinase activity are thought to be involved in ibuprofen's beneficial effects in ventilator-induced lung injury. In humans, the use of a Rho kinase inhibitor has not been confirmed to have severe hemodynamic side effects, and it has been shown to have excellent tolerability. Based on post-market monitoring, haemorrhage (1.7 percent) and hypotension were the most frequent adverse effects recorded for fasudil (0.07 percent). Rho kinase inhibitors' protection profile may be their most significant benefit in the care of acute lung inflammation acute lung inflammation (ALI). However, since these inhibitors are multifunctional, they seem to be more beneficial than any other medicinal agents utilised in the care of ALI. Rho kinase inhibitors have been shown to improve cell viability in several *in vitro* trials. In our search of the literature, we identified no single report that contrasted the effectiveness and/or risks of Rho kinase inhibitors to those of other therapeutic agents. Human evidence and clinical trials confirming the beneficial effects of Rho kinase inhibitors in ALI are minimal or non-supportive, despite preclinical studies endorsing the beneficial effects of Rho kinase inhibitors in ALI. For example, in the case of sepsis and inflammatory diseases, around 150 compounds reached clinical trials based on preclinical evidence, none of which were Rho kinase inhibitors, but failed to hit the market, indicating the need for improved preclinical efficacy protocols. Finally, it appears that up regulation of the RhoA/ROCK signalling pathway is essential in the pathogenesis of ALI.

Rho kinase inhibitors have shown in limited preclinical studies to have a high potential for preventing the development of ALI. Inflammation, immune cell migration, apoptosis, coagulation, contraction, and cell adhesion were all inhibited, which had positive effects.

Endothelium barrier impairment and edoema was reduced as a result of increased pulmonary endothelial cells. Inhibition of Rho kinase seems to be a successful new method for treating ALI [ARDS]. However, more clinical trials are needed to back up this hypothesis [44].

p38 MAP kinase inhibitors in signalling pathways as possible neuroprotective drugs were studied by Ahmed et al. The discovery of p38 MAP kinase's connection to TNF- and IL-1 synthesis in 1994 established the fact that the net biological effect of p38 activation is the downstream development of various inflammatory mediators that initiate the activation and recruitment of leukocytes. p38 MAP kinase signalling is linked to excitotoxicity (glutamine aggregation in synapses) in astrocytes, synaptic plasticity, and tau phosphorylation in neurons, and it leads to neuroinflammation. The activity of the p38 MAP kinase may play a role in the pathophysiology of a variety of neurodegenerative disorders, including Parkinson's disease (both hereditary and sporadic) and multiple sclerosis. There are four different isoforms of the p38 MAP kinase, all of which share roughly 60%

homology. The p38a MAP kinase is a major isoform of p38 that is activated under inflammatory conditions and is a key player in the synthesis of inflammatory mediators. Upstream MAP3Ks normally trigger downstream MAP kinases (MKK3 and MKK6). MKK3 and MKK6 trigger p38 MAPK through dual phosphorylation on Tyr182 and Thr180 once enabled. In neurodegenerative diseases, p38 MAP kinase may control hyperphosphorylation of Tau (PHFTau), leading to its dissociation from the cytoskeleton and self-aggregation. PHF-Tau is a significant component of the neurofibrillary tangles, which are one of the most common aberrant forms seen in Alzheimer's cases. In the astrocytoma cell line U373 MG, p38 MAP kinase mediates substance P (SP)-induced IL-6 expression independently of NF-B activation. SP caused p38 MAP kinase phosphorylation, which was independent of p42/44 MAPK and protein kinase C activation [45]. Gordon et al. found that stimulation of protein kinase c delta in response to neurotoxic stressors (a-synuclein, TNF-, LPS) plays a crucial role in the induction of dopaminergic neuronal failure. Protein kinase c delta deficiency was shown to reduce locomotor deficiencies and decrease proinflammatory reaction in the mouse substantianigra in an experimental model of Parkinson's disease. The function of p38 MAP kinase inhibitors in the treatment of neurodegenerative disorders has been investigated, with a particular emphasis on their regulatory pathways [46]. According to Lund et al., CEP-1347 inhibits cytokine synthesis in human or murine microglia primary cultures as well as monocyte or macrophage-derived cell lines stimulated with Ab140 or endotoxins. The MLK inhibitor CEP-1347 inhibited the activation of the cJun/JNK signalling pathways in stressed neurons.

CEP 1347
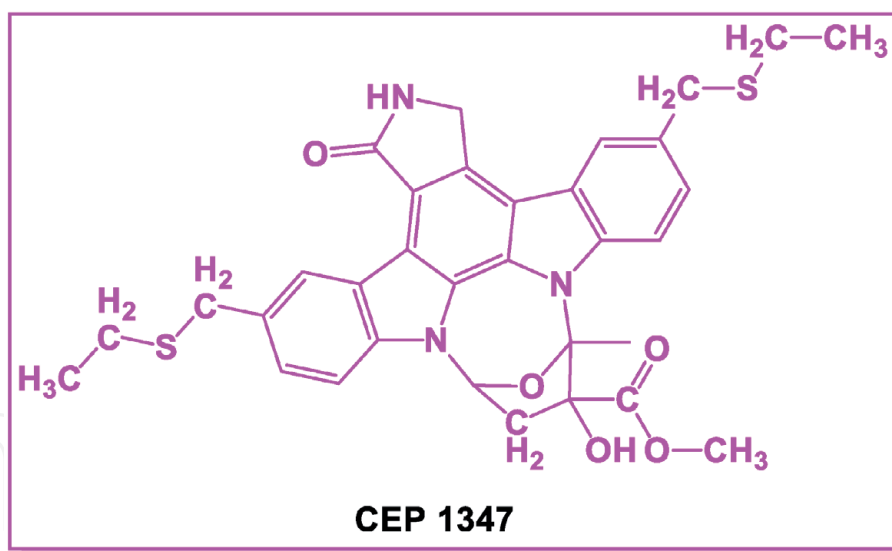
In PD animal experiments, the inhibitor also reduced neurodegeneration. It is important to provide a thorough understanding of the signal transduction mechanisms involved in microglia-mediated inflammation in order to find therapies that can be used to cure neurological disorders. The p38 MAP kinase inhibitors and JNK signalling pathways specifically allow a better choice to be investigated further due to their potential to decrease proinflammatory cytokines production and their intracellular signalling pathway [47]. Watts et al., [48] and Wu et al., [49] recently published studies that say MAP4K4. According to Wu et al. [49], factors secreted in motor neuron cultures trigger MAP4K4.Following MAP4K4 activation, motor neurons die. As a result, MAP4K4 reduction will affect motor neuron viability through I attenuation of the c-Jun apoptotic pathway, and (ii) activation of autophagy mediated by FoxO1 that reduces protein aggregate accumulation and depicts that

the activation of the p38 MAP kinase pathway in various cell types and pathways in neurodegenerative diseases.

10. Differential modulation of phosphorylation

In a single cell method, Basken et al. used phosphoproteomics to compare molecular responses to inhibitors that target protein kinases in several tiers of the MAPK cascade. They learned a lot regarding oncogenic BRAF signalling in melanoma cells, as well as new knowledge about MAPK pathway organisation, phosphorylation specificity, and off-target responses to therapeutics that are currently in use or being developed. The following results may be drawn from the study's findings:

First, there is a lot of variation between the phosphosites that are substantially influenced by MKK1/2 and ERK1/2 inhibitors. There were no answers that were specific to MKK1/2 or ERK1/2 inhibitors. This indicates that the signalling system is mostly absent of MKK1/2 targets that split upstream of ERK1/2. Comparing the BRAF inhibitor vemurafenib to the MKK1/2 inhibitor selumetinib in a previous analysis from our lab revealed identical results. The observed results suggest that signalling downstream of oncogenic BRAF requires a linear organisation of protein kinases, from BRAF to MKK1/2, and from MKK1/2 to ERK1/2, rather than a bifurcation in the pathway.

Second, the 161 sites controlled by all four MKK1/2 and ERK1/2 inhibitors revealed phosphorylation sites most likely to be bona fide targets of the MAPK pathway, allowing us to recognise phosphorylation sites most likely to be bona fide targets of the MAPK pathway. Moreover, hundreds of phosphosites have been identified as possible new ERK targets. Just 20% of the 103 phosphosites with Ser/Thr-Pro sequence specificity for ERK met existing ERK targets, implying 82 additional direct phosphorylation targets. A subset of 47 previously unreported phosphosites is prioritised as probable ERK1/2 substrates by searching for markers of MAPK substrates, such as proximity to Pro at position P-2 and the inclusion of DEF or DEJL docking motifs. The importance of this study is that, considering the fact that more than 700 ERK phosphorylation sites have been identified *in vitro* and/or *in vivo*, the amount of sites yet to be found is uncertain. The use of phosphoproteomics to find new substrates is hampered by a lack of understanding of kinase inhibitor specificity, as well as the risk of off-target results. Where a pathway signals linearly, as tends to be the case with the enzymes in the MAPK pathway, contrasting the coordinated effects of several inhibitors on more than one tier of the kinase cascade, as well as sequence determinants of ERK substrates, offers a rigorous filter for specificity. The findings indicate that ERK1/2 regulates new types of cellular processes, and they add for understanding of the pleiotropy of cellular responses that this important signalling kinase may influence.

Third, they discovered that 21 of the phosphosites observed to react to at least one of four kinase inhibitors only reacted to one of the four compounds, whilst the other three were obviously unresponsive. This serves as a useful filter for detecting inhibitor off-target results. Surprisingly, the majority of unambiguous off-target phosphosites reacted to the ERK1/2 inhibitor GDC0994, while responses to other kinase inhibitors were scarce. This is something to think about if you're looking at ERK1/2 inhibitors as a way to tackle resistance to BRAF and MKK1/2 inhibitor combinations. The inhibition of MKK6 by the clinically important MKK1/2 inhibitor trametinib suggests that even a single off-target may be significant. Depending on the cell type or stimulus, blocking the p38 MAPK pathway may influence survival by promoting oncogenic or tumour suppressive results. Despite the fact that trametinib's IC_{50} for p38 MAPK inhibition was higher than that of MKK1/2-ERK1/2,

this concentration range is often used in literature studies. SB203580, a p38 MAPK inhibitor, increased the cell inhibitory response to selumetinib, implying that inhibiting p38 synergizes with MKK1/2 inhibitors to compromise cell viability in melanoma cell lines. CA-MKK6 and p38 MAPK signalling have been shown to shield melanoma cells from UV-induced apoptosis, according to previous research. When SB203580 was combined with trametinib, the synergistic impact was reduced, which we believe is due to trametinib's off-target influence on MKK6. The findings indicate that trametinib's impact on p38 MAPK may enhance the drug's effectiveness in some circumstances.

Finally, they discussed the problem of differential modulation of phosphorylation targets downstream of BRAF-MKK-ERK signalling. Different proteomics studies sometimes see differences in phosphosite responses to the same pathway, but cannot differentiate if such results are due to unequal signalling responses or experimental heterogeneity. The findings revealed that various cell systems had different reactions to the same pathway. However, some of the reported inconsistencies may be explained by methodological differences between laboratories or off-target inhibitor results, which the study could not rule out. The authors were able to re-address this issue more rigorously after comparing four inhibitors using data obtained by one lab in one cell system. Finally, it was discovered that certain, but not all, validated ERK1/2 targets are protected from phosphorylation in cell system. The significance of this discovery is that nothing is known regarding why certain phosphorylation sites that are usually supervised by ERK are bypassed under some conditions but are repeatedly attacked under others. Awareness the processes that regulate variability in cellular responses may include an understanding of the fundamental mechanisms that contribute to differential regulation within the phosphoproteome. The gain of new insight into new targets for control by the oncogenic BRAF driver pathway in cancer cells by comparing different inhibitors of multiple kinase tiers utilising phosphoproteomics, which is a valuable method for assessing the specificity of drugs and drug candidates [50]. The Bender and colleagues have shown that significant effect on CK2 and it has a proliferation and differentiation of neural stem cells from the sub ventricular region in a sample. They reported that proliferative ability is significantly reduced when the enzyme is inhibited [51]. CK2 inhibition interrupts the neuronal and glial lineages within a three-day time window during differentiation. CK2 kinase function seems to be redundant at later levels of differentiation. While it has been established that CK2 plays a role in nervous system production, knowledge on the role of kinase-dependent pathways in neurogenesis is scarce. This may be attributed to the CK2 or CK2 knockout mice's extreme and fatal neurodevelopmental phenotypes. Huillard et al. found that disrupting the CK2 subunit induced oligodendrogenesis to be negatively regulated. The bHLH transcription factor Olig2, which is one of the main regulators of oligodendrocyte growth [52], interacts with CK2. It was also discovered that embryonic stem cells lacking tCK2 had a viability deficiency. They also discovered that CK2 is needed for neurosphere oligodendroglia differentiation. In the absence of CK2, the effect of CK2 is attributed to a defect in the holo enzyme's CK2 kinase activity. Those substrates that are only phosphorylated by the holo enzyme cannot be phosphorylated without CK2. It also explains how Drosophila CK2 is involved in cell proliferation and survival during brain growth. The nucleolar mushroom body miniature (mbm) protein is one of the potential substrates. This protein is thought to be involved in nutrient-dependent signalling processes that regulate ribosomal expression. The observed findings with inhibitors of CK2 kinase activity clearly support the theory that the holo enzyme is the functional type of CK2 involved in neurosphere proliferation and differentiation. Furthermore, hereditary disruption in embryonic neurogenesis results in decreased neural stem cell proliferation and

self-renewal. These results are in line with our findings from postnatal neural stem cells originating from the subventricular region that were inhibited. The issue of lethality can be solved by using knock-down methods or CK2 inhibitors, which allows researchers to explore the postnatal function of CK2 in the nervous system. The function of CK2 in the nervous system may be investigated further using these methods. As a result, it was discovered that CK2 plays a role in ion channel organisation and synaptic transmission [51]. CX-4945 [Silmitasertib] is a powerful inhibitor of CK2's kinase function that was developed as an anticancer medication. CX- 4945 has been shown to have cytotoxic properties in acute lymphoblastic leukaemia cells, inhibit pro survival signalling in human breast cancer cells, and may be used to treat cancer stem cells in glioblastomas. CX-4945 also appears to control osteoblast differentiation *in vitro* and can function as a splicing regulator. CX-4945-treated human mesenchymal stem cells divide into adipocytes in the same way as untreated cells do, according to a new report. The inability to prevent differentiation was shown to be followed by a lack of CK2 kinase inhibitory activity. The function of CK2 in neurogenesis was investigated using CX-4945 in various concentrations. The proliferation of neurospheres is inhibited in a dose-dependent way, according to this research. Since CK2 can be effectively inhibited, two concentrations, 10 and 20 M, were chosen for differentiation experiments. A higher concentration of CX 4945 causes apoptosis, which greatly decreases cell numbers and attacks stem cells and neuronal precursor cells in particular.

CX-4945 [Silmitasertib]
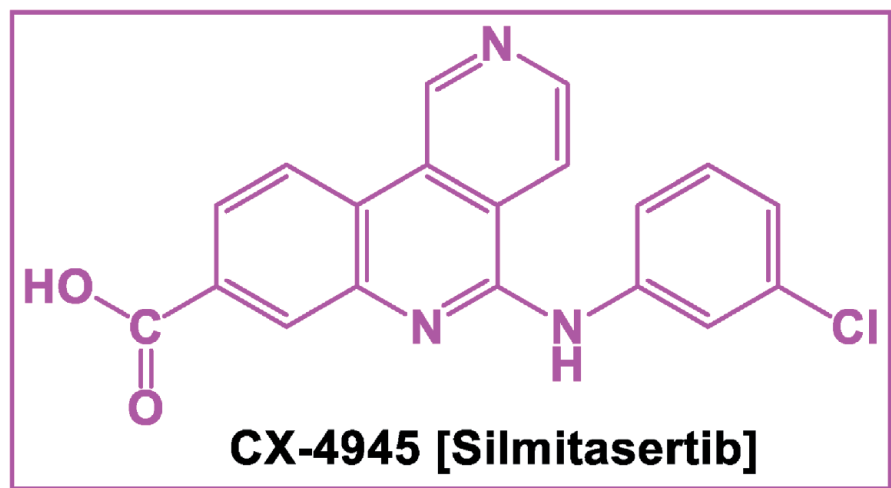
As a result, the effect on neurogenesis at this concentration is due to apoptosis rather than a particular inhibition. Despite this, the remaining cells maintain their cell cycle distribution. We were able to demonstrate that inhibiting CK2 contributes to a significant suppression of neurogenesis as well as a reduction in gliogenesis by focusing on the surviving cells during differentiation. We have also seen that the effect of CK2 persists for many days during separation and that this effect degrades slowly and steadily. The lack of apoptosis was observed when a dosage of 10 M CX-4945 was used, indicating that this concentration is non-toxic. In this scenario, we found that gliogenesis was inhibited but not neurogenesis, indicating that neuronal precursors are more susceptible to apoptosis at higher inhibitor concentrations. Using various concentrations of quinalizarin, they were able to achieve either heavy apoptosis or no inhibition of the CK2 kinase activity. The CK2 kinase function was inhibited by about 40% when 40 M quinalizarin was used. In this event, neurogenesis was inhibited but gliogenesis was not. The findings obtained with the two inhibitors lead me to believe that neurogenesis inhibition is somehow linked to apoptosis activation, whereas gliogenesis inhibition is specifically linked to CK2

inhibition. This hypothesis is confirmed by Huillard and Ziercher's findings, which showed that disrupting CK2 subunit expression causes oligo-dendrogenesis to be negatively controlled. It appears that the period when CK2 kinase activity is needed for differentiation is critical. Although knocking out CK2 in embryonic stem cells causes overall developmental failure, lineage finding can benefit from timely activation or inhibition of the enzyme within a particular organ system, particularly when the enzyme is partially up- or down-regulated. The results indicate that inhibiting CK2 for 1–3 days prevents stem cell differentiation. The interdependencies of the specific partners, such as neurons and glial cells, are also a significant feature of CK2's function in neurogenesis. Glial cells are well known for producing a wide variety of trophic factors and cytokines that can aid in the survival and differentiation of neurons. The current observations in the nervous system are consistent with the osteoclast separation results obtained with CX-4945. Furthermore, CX-4945 was found to suppress RANKL-induced osteoblast differentiation. CX-4945, on the other hand, increased BMP2-induced osteoblast differentiation. Another research looked at the differentiation of pre-adipocytes into adipocytes and found that the activation of the CK2 kinase increased at the start of the differentiation phase and decreased as the differentiation progressed. Furthermore, inhibiting CK2 kinase activity at the start of differentiation for up to 6 days inhibits differentiation, although there was no inhibition of differentiation after day 6. As a consequence, these findings are in strong harmony with the neural differentiation evidence discussed here. Future experiments with graded up- and down-regulations of CK2 will reveal whether CK2 is still active in the differentiation fate decision of neurons and glial cells [51].

Platelet glycoprotein IIb/IIIa inhibitors (GP IIb/IIIa inhibitors) have a well-established thrombolytic role in myocardial infarction. Despite this, there is a scarcity of information on the mechanism of GP IIb/IIIa inhibitors'cardioprotective function in ischemic-reperfusion injury (IR). 120 minutes of coronary ischemia and 180 minutes of reperfusion were provided to Sprague–Dawley rats. PKC (chelerythrine), PI3 kinase and Akt (wortmannin), p38 MAPK (SB203582), p42/44 MAPK (PD98059), and ERK1/2 (u0126) inhibitors were provided by continuous intravenous infusion at a rate of 2 ug/kg/min 30 minutes prior to reperfusion with/ without inhibitors of PKC (chelerythrine), PI3 kinase and Western blot analysis was used to isolate and analyse proteins. The apoptotic index (AI) was determined as the percentage of myocytes positive for terminal deoxynucleotidyltransferase-mediated dUTP-biotin nick-end labelling of all myocytes stained with 4′, 6-diamidino-2-phenylindole and the ratio of myocardial necrotic region to the area at risk (AAR). The GP IIb/IIIa inhibitor decreased the ratio of myocardial necrotic region to AAR and AI, as well as exerting an immediate cardioprotective impact by phosphorylating and triggering multiple signalling pathways such as PKC, PI3 kinase, Akt, p38 MAPK, p42/44 MAPK, and ERK1/2. Raf and MEK1/2 phosphorylation, on the other hand, did not show any major rises. Chang et al., found that inhibiting GP IIb/IIIa decreased the level of cardiac IR and greatly reduced myocyte apoptosis in rats. Furthermore, the cardioprotective influence was induced by several signal transduction pathways activation [53].

Linagliptin-induced vasodilation was studied by Seo et al., in a concentration-dependent manner. The absence of endothelium, as well as pre-treatment with a nitric oxide synthase inhibitor (L-NAME) or a small-conductance Ca^{2+}-activated K^+ channel inhibitor, had little impact on the vasodilatory effect of linagliptin (apamin). Furthermore, the adenylyl cyclase inhibitor SQ22536, the protein kinase A (PKA) inhibitor KT5720, the guanylylcyclase inhibitor ODQ, and the protein kinase G (PKG) inhibitor KT5823 had no impact on linagliptin's vasodilatory effect. Y-27632, on the other hand, greatly reduced linagliptin-induced vasodilation by

inhibiting Rho-associated protein kinase. The function of ion channels in lina-gliptin's vasodilatory effect was also examined. Glibenclamide (ATP-sensitive K^+ channels), Ba^{2+} (inwardly rectifying K^+ channels), 4-AP (voltage-dependent K^+ channels), and paxilline (large conductance Ca^{2+}-activated K^+ channels) were not found to influence linagliptin-induced vasodilation. Furthermore, nifedipine, an inhibitor of L-type Ca^{2+} channels, and thapsigargin, an inhibitor of the sarco-plasmic/endoplasmic reticulum Ca^{2+}-ATPase (SERCA) pump, had no impact on linagliptin's vasodilatory effect. The inhibition of Rho-associated kinase, but not the endothelium, cAMP-PKA or cGMP-PKG-dependent signalling pathways, K^+ chan-nels, Ca^{2+} influx, or the SERCA pump, could be responsible for linagliptin-induced vasodilation [54].

PKCs are thought to control certain pancreatic functions in natural acinar cells, ductal cells, and islets, as well as in disease states such as insulin tolerance, diabetes mellitus, pancreatitis, and pancreatic ductal adenocarcinoma, according to Fleming and Storz (PDA). PKCs control secretory processes in the regular pancreas, as shown by amylase secretion in acinar cells, bicarbonate secretion in ductal cells, and glucagon and insulin secretion in islets. PKCs play a role in the production of insulin tolerance and diabetes mellitus by regulating -cell proliferation and activity, as well as insulin secretion and cell death. PKCs play a crucial role in pancreatic injury and inflammation, as well as trypsinogen activation and basolateral exocytosis, dur-ing pancreatitis. PKCs eventually play a role in the growth of PDA by promoting acinar cell dedifferentiation (PKC) and acinar-to-ductal metaplasia (PKC). PKC control proliferation and promote anchorage-independent development throughout the progression of PDA. Atypical PKCs have also been linked to the regulation of metastasis. In conclusion, PKC isoforms play a variety of roles in normal pancreatic regulation, but they may also play a role in the onset and development of pancreatic disease [55].

Mitochondrial ATP synthase, a significant ATP supply in respiring cells, should be regulated in both quantity and action to react to differing ATP demands. Sugawara et al., screened 80 protein kinase inhibitors and discovered that four of them decreased mitochondrial ATP synthesis function in HeLa cells. Knocking down their target kinases (PKA, PKCd, CaMKII, and smMLCK) consistently resulted in lower mitochondrial ATP synthesis output. The mitochondria of smMLCK-knockdown cells only possessed a limited amount of ATP synthase, whereas the a- and b-subunits of ATP synthase were formed normally, implying that smMLCK affects ATP synthase assembly (or decay) [56].

PIM (proviral insertion in murine) Kinases are a kind of proto-oncogene that phosphorylates the target proteins' serine/threonine residues. PIM-1, PIM-2, and PIM-3 are the three groups that play an important regulatory function in signal transduction cascades by facilitating cell survival, proliferation, and drug tolerance. These kinases are overexpressed in a variety of solid and hematopoietic tumours, supporting malignant cell growth and survival *in vitro* and *in vivo* by controlling cell cycle and inhibiting apoptosis. They are constitutively active until transcribed and they lack a regulatory domain. PIM kinases are thought to be essential down-stream effectors of oncoproteins that overexpress and aid in the mediation of drug resistance to available agents like rapamycin. According to Panchal and Sabina, PIM kinases have special hinge regions where two Prolines exist, which makes ATP bind-ing unique while also providing a focus for a growing array of potent PIM kinase inhibitors. Preclinical trials of such inhibitory compounds in different cancers sug-gest that they have positive efficacy, and some of them are currently being studied. In their study, they described the molecular mechanism and signalling mechanisms of PIM kinases, as well as matriculation in multiple cancers and a list of commonly used inhibitors [57]. Dengue virus (DENV) infection is a disease that is common to

many areas of the world, and its rising incidence places it among the diseases that pose a serious public health danger. Dengue fever (DF), dengue hemorrhagic fever (DHF), and dengue shock syndrome are among the clinical symptoms of DENV infection (DSS). Extreme dengue fever is characterised by increased proinflammatory cytokines and vascular permeability, all of which trigger organ damage. Sreekanth et al. used hepatic cell lines, mouse models, and autopsy specimens from DENV-infected patients to observe symptoms of liver damage, and these signs substantiated the results of inflammatory responses and hepatic cell apoptosis. During viral infections, MAPK are implicated in inflammatory responses and cellular tension. MAPK signalling has been implicated in inflammatory responses and hepatic cell apoptosis in both *in vitro* and *in vivo* models, according to published evidence. In DENV infection, modifying MAPK signalling reduces inflammatory responses and hepatic cell apoptosis. This body of knowledge about the function of MAPK signalling in inflammatory responses and cell apoptosis in DENV infection is illuminating, and it could speed up the creation of new or repositioned therapies to treat this unpredictably disabling disorder [58].

11. Conclusion

In this study, we have addressed the role of protein kinase in human cells and the effects of protein kinase inhibitors in the treatment of various diseases and disorders. Protein kinase is a type of kinase enzyme that adds phosphate groups to other proteins chemically (i.e. phosphorylation). Many biochemical signalling pathways within cells (i.e. signal transduction) and effectors in cellular functions, such as cell proliferation and necrosis, are influenced by this enzyme. Protein kinases are the third messenger mechanism, and most of their isoforms depend on second messengers like cAMP and calcium to function. Overexpression of protein kinase, on the other hand, causes life-threatening diseases such as cancer, cardiovascular disease (hypertension), central nervous system disease, skin disease (inflammation), diabetes mellitus, and so on. Moreover, the findings of various researchers has also added to the fact. There are currently a range of protein kinase inhibitors in the market that inhibit protein kinase activity. They can be used to regulate the cellular responses that protein kinase activity causes. As a result, there is scope for the design and production of new medicines that inhibit protein kinase overexpression for the prevention and treatment of associated disorders. The functions of protein kinases in signal transduction, the effects of overexpression, and the therapeutic roles of various protein kinase inhibitors are all discussed here. As a result, further research into the protein kinase is needed in order to develop more potent and effective prophylactics for disease treatment.

Abbreviations

ATP	Adenosinetriphosphate
ADP	Adenosinediphosphate
PTMs	Post-transitional modifications
JAK	Januskinase
MAPK	Mitogen-activated protein kinase
CDKs	Cyclin-dependent kinases
Abl	Abelsonmurine leukaemia virus
MKK4	Mitogen-activatedproteinkinase4
AMPK	AMP-activated protein kinase

VEGFR	Vascular endothelial growth factor receptors
EGFR	Epidermal growth factor receptors
NAFLD/NASH	Non-alcoholic fatty liver disease/Non-alcoholic steatohepatitis
LRRK2	Leucine-richrepeatkinase2
NO	Nitricoxide
PKI	protein kinase inhibitor
ALI	Acute lung inflammation acute lung inflammation
ERK	Extracellular signal related kinase
PD	Parkinson's disease

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