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Effect of Phytocannabinoids in the Modulation of Thrombosis and Haemostasis

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Background:

During lead identification and optimization, the advancement criteria may be driven based on scientific principles, prior experiences, and/or by examining the path paved by approved drugs. However, accessing the discovery data on physicochemical and ADME properties of the approved kinase inhibitors is a monumental task as these are either scattered in the literature or have not been published.

Objective: Our goals were:

1) To compile the relevant data on all kinase inhibitors approved prior to 2016 for easy access by the biopharmaceutical community, 2) To provide a retrospective analysis to highlight trends and attributes which may have contributed to the "developability" of these drugs, and 3) To ignite focused debates on what constitutes "actionable", "nice-to-have", and unnecessary data. Such debates bring about more clarity on stage appropriateness of different types of information and prevent confusion due to abundance of unnecessary data, leading to more efficient and less costly drug discovery programs.

The Philadelphia Chromosome was the result of reciprocal translocation of chromosomes 9 and 22, generating an elongated chromosome 9 and a truncated chromosome 22. The translocation juxtaposes the Abl1 gene on chromosome 9 to a part of the BCR on chromosome 22 and leads to CML. The translocated Abl1 gene, which encodes a tyrosine kinase, causes deregulated and continual overexpression of kinase activity resulting in tumor development. From this landmark discovery, it became evident that many human malignant diseases were associated with mutations, chromosomal rearrangements and/or overexpression of protein kinases [11, 13-16]. This discovery quickly led to protein kinases becoming well accepted targets for anticancer drug development [17-24]. During late 1980s and early 1990s, tremendous efforts were made to unfold the intracellular signal transduction pathways and aberrations of signaling pathways leading to variety of diseases at the genetic and molecular levels [25-30]. Many extra- and intra-cellularly associated kinases, such as MAPK, ERK, JAK and PI3K, were reported to regulate normal cellular functions [31, 32]. So far, a total of 518 human kinases and 900 human genes encoding for kinase proteins have been revealed [33]. In the meantime, it has been discovered that deregulation and/or over-expression of certain types of kinases lead to changes in the normal cellular functions which further advance to disease states. Platelets are small circulating blood cells that play primary roles in the maintenance of haemostasis through blood clotting. Inappropriate activation of platelets in pathological conditions results in thrombosis under arterial circulation causing an obstruction of the blood flow to major organs like heart and brain resulting in myocardial infarction and stroke, respectively. While the currently used anti-platelet drugs help saving lives, they're related to unwanted side effects. Hence, the event of improved therapeutic strategies to treat/prevent thrombotic diseases may be a pressing priority. Non-psychoactive phytocannabinoids like cannabidiol (CBD) from marijuana plant are demonstrated to possess numerous beneficial effects in distinctive pathological conditions. Therefore, during this study, we investigated the consequences of CBD and its precursor molecule cannabigerol (CBG) within the modulation of platelet function, thrombosis and haemostasis. Both CBD and CBG (at concentrations of 1-100μM) inhibited significantly agonists utilized in this study (CRP-XL, thrombin, ADP, U46629 and collagen) in platelet function like aggregation, fibrinogen binding, P-selectin exposures and ATP secretion. Moreover, CBD and CBG did not exert any cytotoxic activities at the concentrations used in this study. The data obtained in this study demonstrate that CBD and CBG have the potential to modulate platelet function through inhibiting multiple agonists-induced pathways at concentrations of less than 10μM. Together, our results suggest that CBD and CBG may act as potential therapeutic agents to treat/prevent thrombotic diseases.

Methods:

A careful and thorough analysis of different bodies of data such as published manuscripts, and available regulatory documents were employed.

Conclusion:

In conclusion, we have compiled physicochemical and ADME data on the first 30 approved kinase inhibitors and provided our retrospective analysis, which we hope is helpful in constructing advancement criteria in discovery programs. The examination of this data provides an opportunity to develop an opinion on data prioritization and stage appropriateness of assays.

Note: This work is partly presented at 16th Global Summit on Toxicology & Applied Pharmacology October on 15-16, 2018 held at Las Vegas, USA