

# Investigation of anti-angiogenesis drugs as anti-cancer agents

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## Introduction

The investigation of the properties of anti-angiogenesis drugs tranilast and combretastatin A4 Phosphate, as mitochondrial inhibitors into new mechanisms of action of anti-cancer therapeutics. Angiogenesis has become a key target into developments within cancer research. The aim of the study is to investigate the effects of anti-angiogenesis drugs on mitochondrial function with the hypothesis that some of these drugs may cause mitochondrial type 2 apoptosis, which is generally absent or dysfunctional in cancer cells [1]. Angiogenesis is a physiological process involving the growth of new blood vessels from pre-existing vessels. It is an essential and normal process in wound healing, tissue growth and development. In addition, angiogenesis is a fundamental stage in the transition of tumours from a pre-malignant to a malignant state that is needed to form a network of new blood vessels for supply of oxygen and nutrients to tumour tissues. In normal healthy tissues the balance of pro-angiogenic and anti-angiogenic growth factors and proteins favours inhibition of angiogenesis. As new capillaries are needed, the balance of growth factors is adjusted to stimulate vascular growth. The major critical activator of angiogenesis is a pro-angiogenic growth factor (vascular endothelial growth factor – VEGF) with the latest treatment for different tumours being Avastin™ with the mechanism of the action of the compounds poorly understood. Angiogenesis is heavily dependent on energy in the form of a chemical Adenosine 5' Triphosphate (ATP); which is made in small sub-cellular organelles called mitochondria. It is needed for both the DNA and protein synthesis needed for new blood vessels to form. The chemical structures of several compounds that inhibit angiogenesis have structural similarity with compounds already shown to inhibit mitochondrial function [2,3,4].

## Hypothesis

Our hypothesis is that some angiogenesis inhibitors such as tranilast and combretastatin A4 have a direct effect on mitochondrial function. If our hypothesis is correct, this may shed new light on how certain anti-cancer medicines work, and, may lead to the development of a whole new range of anti-cancer drugs, for use in man and other animals.

## Materials and Methods

Freeze thawed bovine heart mitochondria were incubated with a range of concentrations (0 – 200 $\mu$ M) of various drugs for 5 minutes at 37°C to allow for drug binding. Samples were then pipetted off from the anti-angiogenic drug/mitochondria suspensions and added to separate assay plates containing all the assay components needed for the assay of mitochondrial complex I activity, mitochondrial complex II-III activity or mitochondrial complex IV activity. Mitochondrial complex I activity, II-III activity and complex IV activity was measured in a 96 well plate reader using spectrophotometric methods developed by Dr. Bates [2,3,4].



The shows image shows a pellet of highly purified pig heart mitochondria used in the experiments.

The mitochondria were isolated using homogenisation and differential centrifugation.

## Results

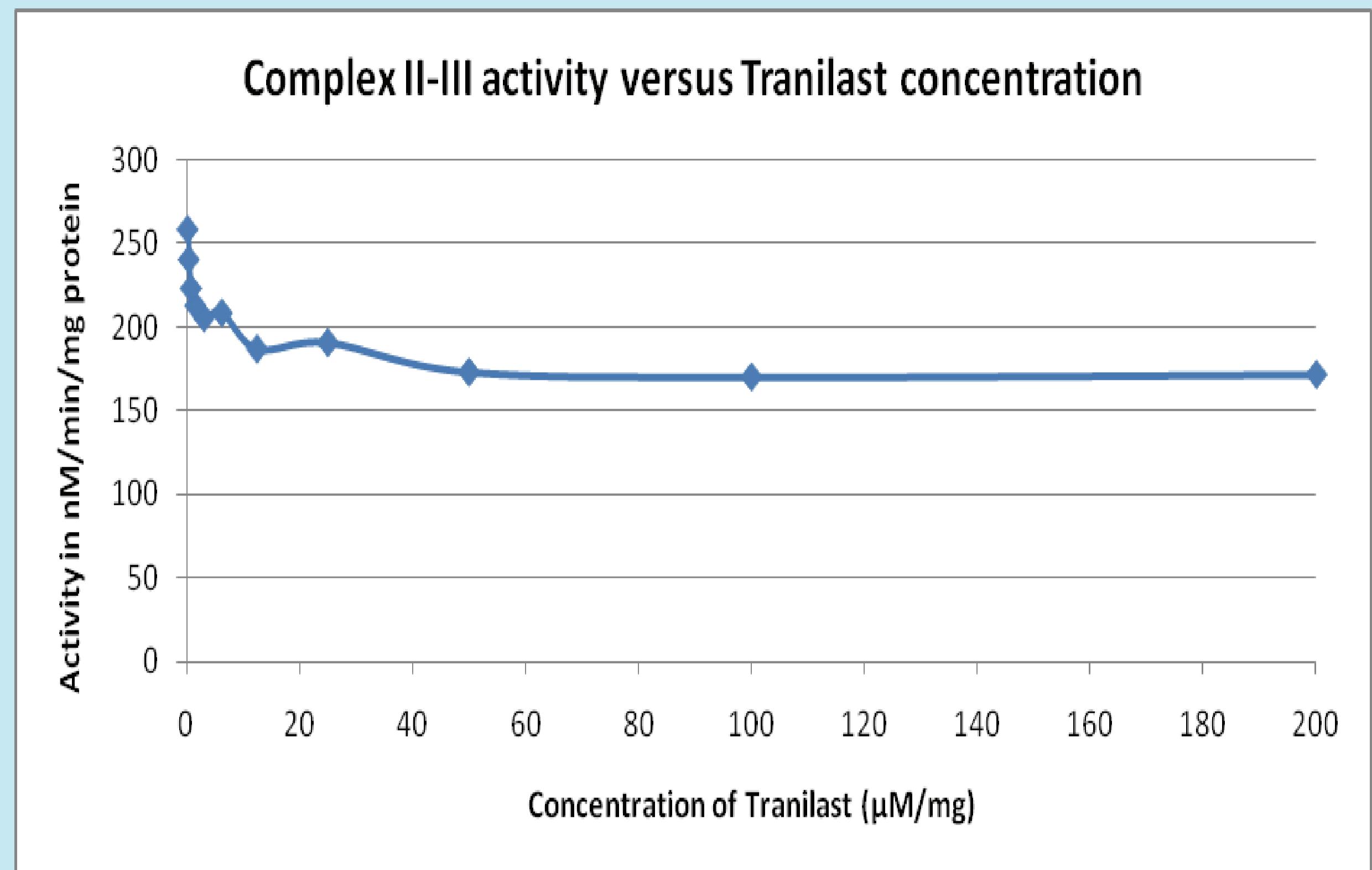


Figure 1: Graph showing an inhibition of mitochondrial complex II-III activity in the presence of Tranilast.

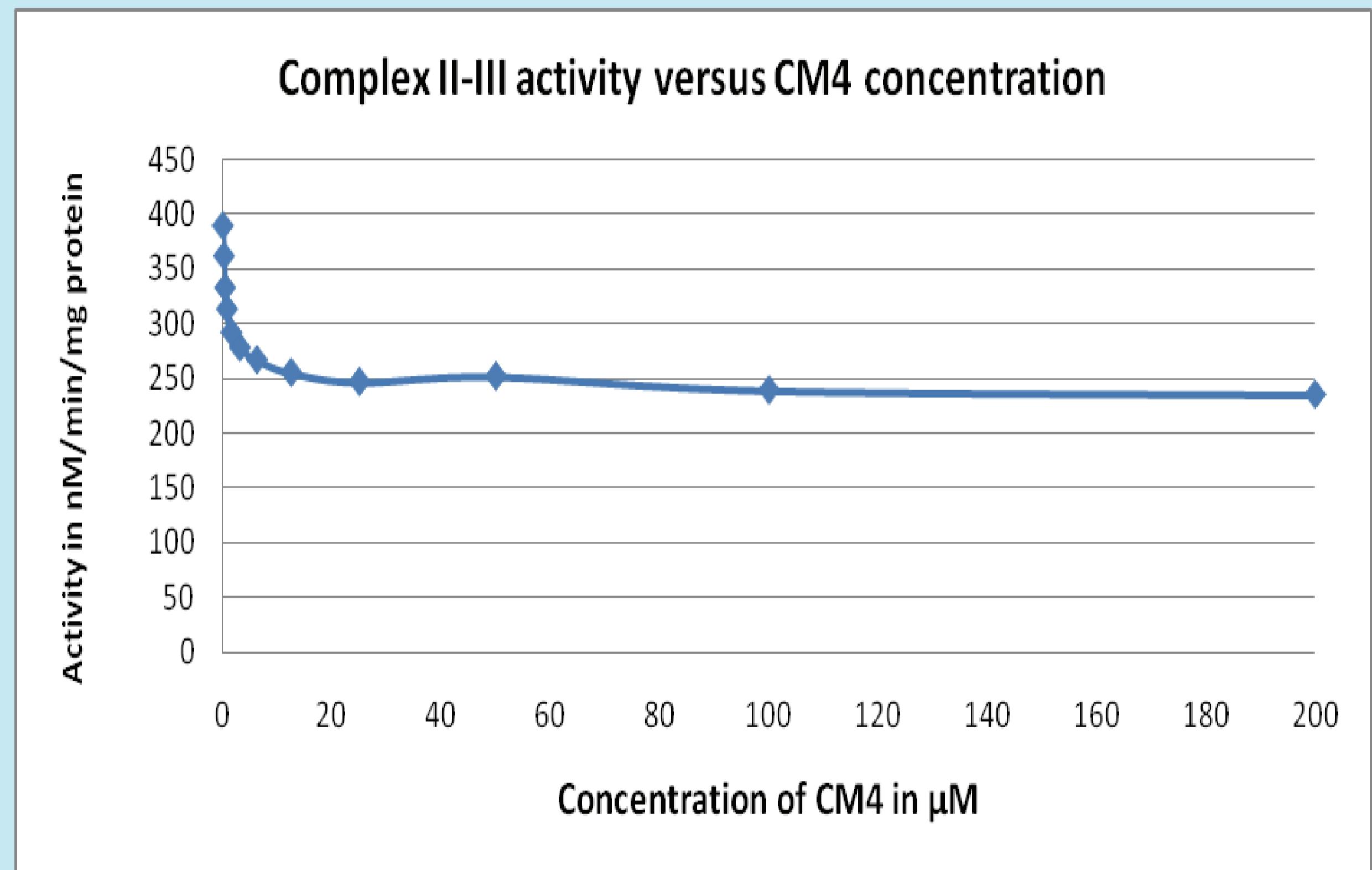


Figure 2: Graph showing an inhibition of mitochondrial complex II-III activity in the presence of Combretastatin A4.

## Conclusion

Anti-angiogenic drugs such as combretastatin A4 and tranilast clearly have potent anti-mitochondrial activities, which may be the major route by which these compounds initiate cancer cell death by extrinsic (mitochondrial) apoptosis/programmed cell death. This has major implications for the design of novel anti-cancer drugs as the established mechanisms of action of anti-angiogenic drugs may in fact be due to inhibition of mitochondrial energy metabolism rather than their effects on cytoskeletal proteins. The data is likely to strongly influence the decisions made by pharmaceutical companies in their medicinal chemistry projects, as they strongly suggest that major efforts should be made to design molecules with the ability to bind to and inhibit mitochondrial enzymes, rather than inhibit cytoskeletal protein synthesis and assembly.

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