Understanding the mechanism behind the action of phytochemicals in interacting with the biological system during cancer chemotherapy induced immunosuppression and their significance in modulating the immune system and inflammatory mediators

Introduction

The toxic effects and long-term sequelae of cancer chemotherapy remains a major concern for both patients and clinicians regardless of their curative effect and efficacy (1). Chemotherapy associated malnutrition is yet another massive long standing root cause affecting patients' health (2). The current approaches to counteract the sphere of side effects induced by chemotherapy agents are often completely ineffective. Hence, new and effective combinational therapeutic approaches to ameliorate tolerance and prevent late sequelae of chemotherapy are promptly needed that could improve the overall quality of patient survival. Pharmaceuticals and nutritional sciences have recently witnessed the emergence of a new research field studying the impact of nutrition on human, and animal health. There has been a virtual explosion of interest in identifying foods, food extracts, and phytochemical formulations from plant sources that are able to mitigate oxidative and inflammatory stress. The frequent consumption of fruits can boost our health, and help to prevent diseases. Camachille (*Pithecellobium dulce*) is one of the richest sources of proteins, fats, carbohydrates, calcium, phosphorous, iron, sodium, potassium, vitamin A, thiamine, riboflavin, niacin, and ascorbic acid and contains plethora of phytonutrients like naringenin, tocopherol, gallic acid, catechin, quinine, epicatechin, caeffeic acid, epigallocatechin, myricetin, quercetin, luteolin, apigenin, kaempferol, rutin, hesperetin, shikimic acid, genistein etc (3).

Objectives

Objective 1: To investigate the multifocal role of camachille phytochemicals in modulating cancer chemotherapy associated complications.

Objective 2: *In silico* studies on interaction of camachille phytochemicals with vital signaling proteins in biological system.

Materials and methods

For achieving the **objective 1,** we had designed experiments to investigate the impact of camchille and its phytochemicals in reducing the side effects during cancer chemotherapy and to prove experimentally the impact of camchille in mitigating the complications such as myelosuppression, organ damage and anaemia during cancer chemotherapy.

Parameters taken for investigation:

1. *Haematological parameter analysis 2. Tissue antioxidant status determination 3. Tissue stress marker level analysis 4. Cytokine profiling 5. Serum hepato and nephron toxicity marker analysis 6. Histopathology analysis*

For achieving the **objective 2,** we had designed experiments to prove that camachille phytochemicals and its role in regulating vital signaling proteins in the biological system. For this *in silico* docking studies were performed.

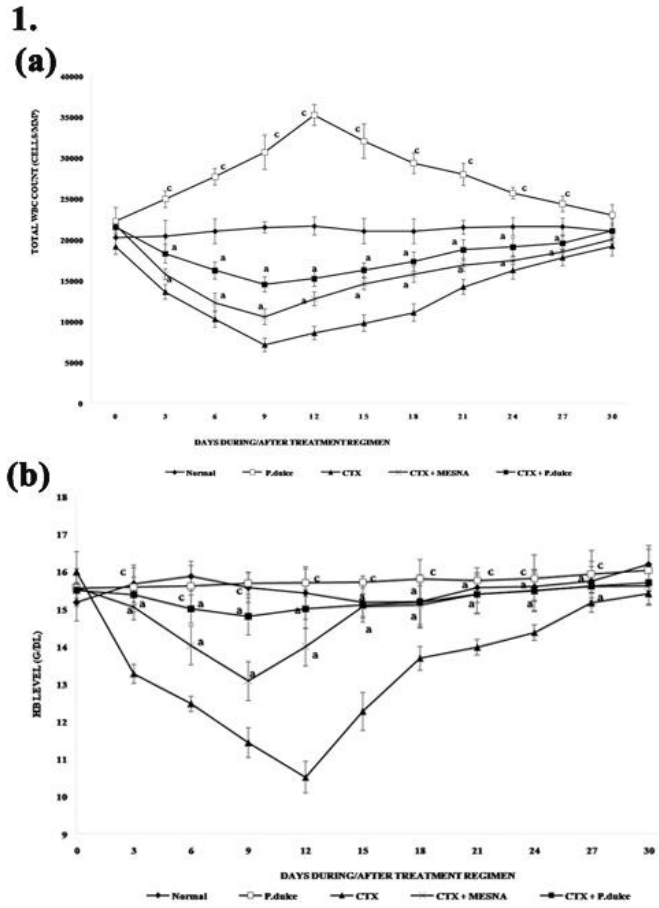
Parameters taken for investigation:

1. Swiss target prediction tool was used to identify potential target of major phytoconstituent (naringenin) 2. Docking studies by Schrodinger maestro suite

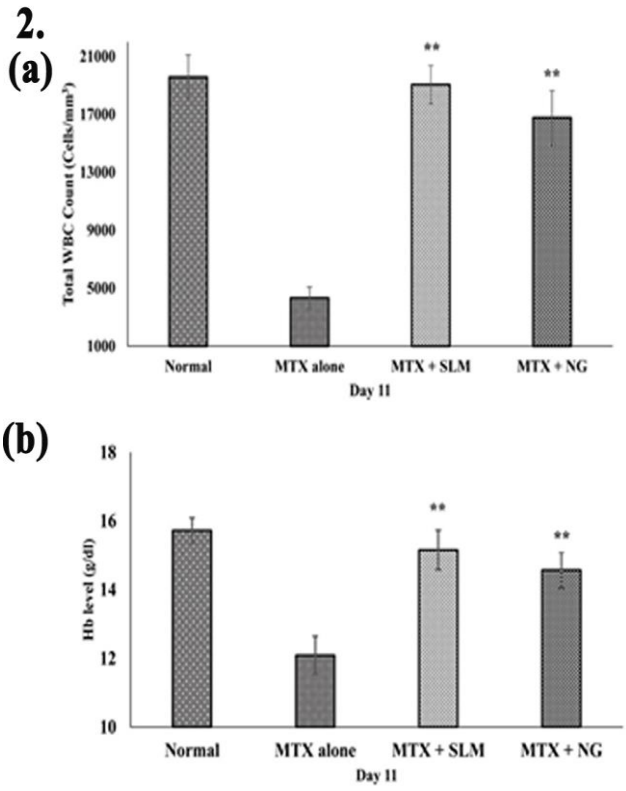
Results

***Key findings after completion of Objective 1 studies*:**

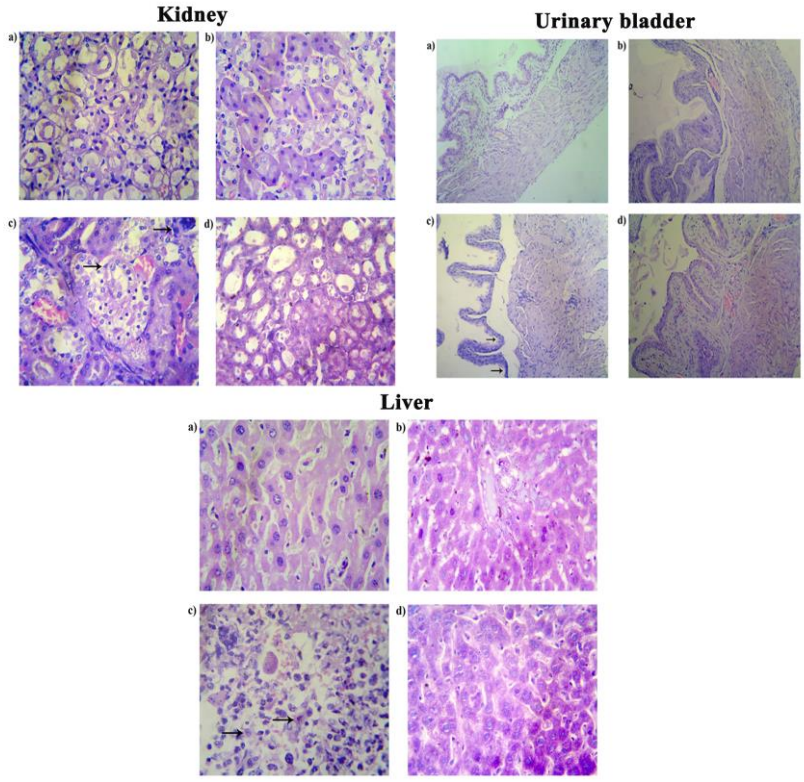
Heamatological parameter analysis



Heamatological parameter analysis



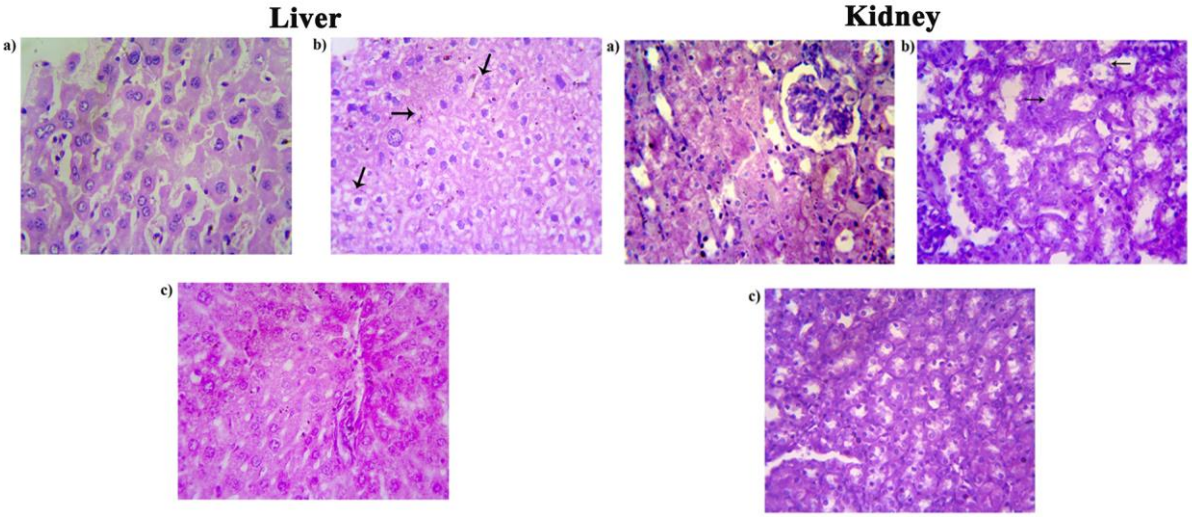
(3)



(a) Normal (b) Camachille alone (c) CTX alone (d) CTX+Camachille

Effect of camachille on different tissues after CTX administration

(4)

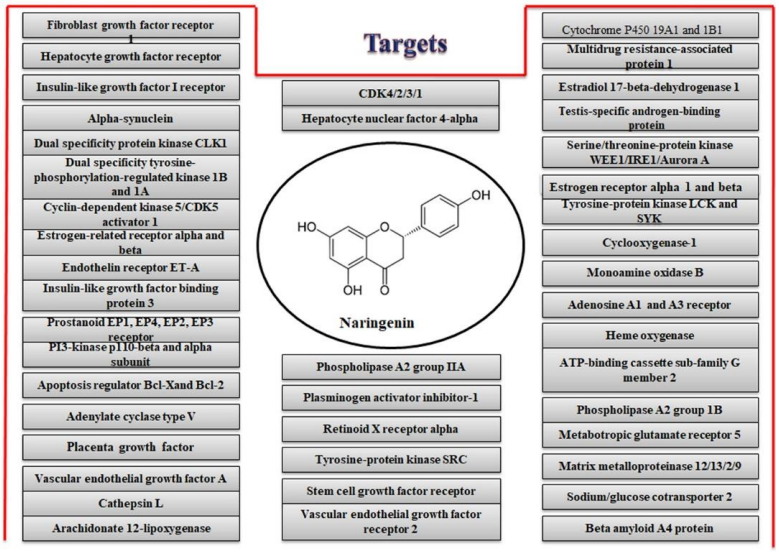


(a) Normal (b) CTX alone (c) CTX+Naringenin (major phytoconstituent of Camachille)

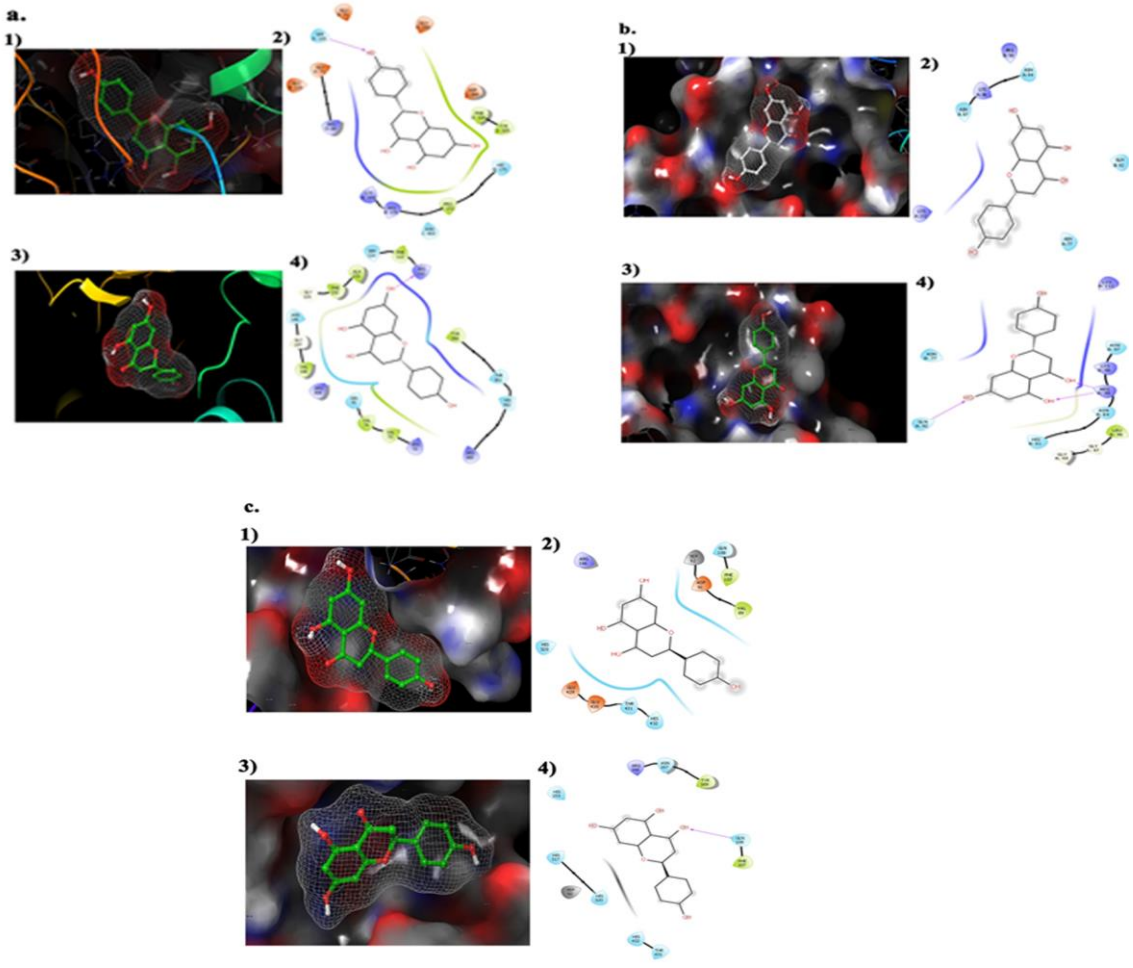
(5) ***Key findings after completion of Objective 2 studies*:**

(6)

Target prediction analysis



Docking analysis



Schematic representation showing interaction of naringenin (S-NG and R-NG) with a. a.1: Interaction complex formed between catalase protein and ligand S-NG 2: Interaction diagram of catalase protein and ligand S-NG.The violet arrow mark denotes hydrogen bond.3: Interaction complex formed between catalase protein and ligand R-NG 4. Interaction diagram of catalase protein and ligand R-NG. The violet arrow mark denotes hydrogen bond.b. 1. Interaction complex formed between GPx(Glutathione peroxidase) protein and ligandS-NG 2. Interaction diagram of GPx protein and ligand S-NG 3. Interaction complex formed between GPx protein and R-NG 4. Interaction diagram of GPx protein and ligand R-NG.The violet arrow mark denotes hydrogen,bond. c.1. Interaction complex formed between ALP (Alkaline phosphatase) protein and ligand S-NG 2. Interaction diagram of ALP protein and ligand S-NG 3. Inter-action complex formed between ALP protein and ligand R-NG 4. Interaction diagram of ALP protein and ligand R-NG. The violet arrow mark denotes hydrogen bond. d.1. Interaction complex formed between SGPT (Serum glutamic pyruvic transaminase) protein and ligand S-NG 2. Interaction diagram of SGPT protein and ligand S-NG.The blue arrow mark denotes hydrogen bond. 3. Interaction complex formed between SGPT protein and ligand R-NG 4. Interaction complex formed between SGPT protein and ligand S-NG. The blue arrow mark denotes hydrogen bond.

Discussion

Phytochemicals and derivatives present in plants are promising options to improve treatment efficiency in cancer patients and decrease adverse reactions. Camachille phytochemicals exert broad spectrum of actions on different molecular and signaling pathways. This study could experimentally prove the potential of camachille phytochemicals in reducing detrimental effects and improving the quality of life during cancer chemotherapy. Our research so far suggests the possible nutraceutical application of camachille and its phytochemicals as potential dietary chemopreventives.

Benefits to mankind

Cancer chemotherapy associated complications deteriorates the patients' Quality of Life (QoL). Major complications associated with cancer chemotherapy such as myelosuppression, organ damage and anaemia during cancer chemotherapy can be confidently addressed using our approach. Apart from alleviating the side effects of chemotherapy, our results show that camachille and its phytochemicals could increase the life span as well as potential enough to reduce the tumour burden. Understanding the mechanism behind the action could result in identification of new molecules or therapeutic combinations that could address a wide range of complications arising during tumour development and associated treatments.

Reference

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2. Gebremedhin TK, Cherie A, Tolera BD, Atinafu BT, Demelew TM. Prevalence and risk factors of malnutrition among adult cancer patients receiving chemotherapy treatment in cancer center, Ethiopia: cross-sectional study (2021). Heliyon. 7(6), e07362.
3. Dhanisha SS, Drishya S, Mony RP, Guruvayoorappan C. (2021). Polyphenolic-rich fraction of Pithecellobium dulce attenuates methotrexate-induced oxidative stress and associated tissue injury by regulating the TNF-α, IL-1β and IL-6 pro-inflammatory cytokines. International Journal of Functional Nutrition. 2, 7.