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The Modulatory Effects of Statins, Vitamin E, and Moringa Oleifera Extract on CD3 Expression in Ribociclib-Induced Hepatotoxicity in Rats

ABSTRACT

Background: The use of Ribociclib leads to hepatotoxicity that may be evaluated by the presence of infiltrated CD3 cells. **Objective:** To evaluate the expression level of CD3 in the liver tissue of the control group and other groups exposed to Ribociclib and groups received Ribociclib and other treatments including vitamin E, statin, and and Moringa Olifera. **Methods:** This experiment utilized fifty adult male albino rats (9 – 10 weeks old). The rats were randomly assigned into five groups (N = 10). Rats in the Group 1 (control) were given 2 ml normal saline. Group 2 rats received 5 mg/kg of ribociclib, while Group 3 rats received the same dose of ribociclib in conjunction with a daily dose of 200 mg/kg of a statin. Group 4 rats were given ribociclib treatment, alongside a daily dose of Vitamin E. Group 5 rats were given daily doses of 5 mg/kg ribociclib and a 200 mg/kg extract of Moringa Olifera. Following the end of the experiment, all rats were terminated and the liver tissues wee excised and fixed in formalin for 24 hours, processed, and stained for CD3 using indirect immunoperoxidase stain. Liver tissues were examined microscopically and the expression level was evaluated employing Adope photoshop. The relationships between groups were computed by independent T test. **Results:** The study showed ribociclib caused hepatotoxicity of liver through the increased expression of CD3 in comparison to the control group. Treatment with statin and vitamin E lowered the expression of CD3, but this was not statistically significant ($p>0.05$), while the treatment with Moringa Olifera extract lowered significantly the expression of CD3 in the liver ($p=0.043$). **Conclusion:** Giving Statin, Vitamin E, or Moringa Olifera extract can protect the liver from the liver toxicity that ribociclib causes.

Keywords: Ribociclib, Hepatotoxicity, Statin, Moringa Olifera Extract, CD3.

1. BACKGROUND

Introduction to Ribociclib-Induced Hepatotoxicity

The advancement of cancer therapy led to developing targeted drugs that have a considerable potential to prolong the lives of patients with certain disease subtypes, such as targeted CDK4/6 inhibitors (1). Hepatotoxicity is one of the most important adverse effects that could limit the use of many of these drugs (2). Hepatotoxicity of these drugs can happen at different exposure levels and could have different injury patterns ranging from moderately increased liver enzyme levels to catastrophic liver failure (3). The mechanisms by which targeted CDK4/6 inhibitors are hepatotoxic are not yet understood (4). Nevertheless, it is hypothesized that hepatocyte injury is likely the primary mechanism underlying liver damage induced by ribociclib (5).

Ribociclib selectively works in addition being orally bioavailable inhibitor of CDK4 and CDK6 that exhibits an irreversible inhibitory effect on CDK4/6 activity along with cellular proliferation (6). Ribociclib has been found to be effective as a first line for progressive breast cancer therapy, improving progression-free survival when used in conjunction with endocrine treatment, and has been approved by the American Food and Drug Administration (FDA) (7). Hepatotoxicity has been reported as an abnormal vital sign in 9.8% of cancer patients treated with ri-

bociclib, and its severity has even been rated as high in laboratory investigations (8). An estimate of incidences in clinical monitoring showed moderate and very late increase in liver enzyme levels (ALT, AST, and ALP) (9). Assessment of exposure suggested that the moderate increase in AGP and overall protein liver enzyme levels corresponded to the lower doses (10). Additionally, liver injury closer to the central vein would be a sign of acute catastrophic liver failure (11).

Role of CD3 Expression in Hepatotoxicity

The immune system is a very complicated that consists of specialized cells, tissues, and organs working to protect the body from any harmful antigens (12). The adaptive immune system, which enables B-cell and T-cell immune responses, is essential for the body's defense mechanisms (13). Recognition of antigens involves the activation of specific T-lymphocytes following binding to MHC/peptides and occurs through the T-cell receptor complex (TCR) (14). In turn, the TCR complex includes two chains, α-chain, and β-chain, in which TCRαβ forms a complex with CD3 (15). CD3 also contributes to TCR maturation, cell surface expression, and antigen recognition by binding to TCR and maintaining T-cell activation (16). CD3 consists of a signaling complex that lies downstream of the TCR and contributes to T-cell development, activation, and subsequent intracellular signaling (17). Given that TCR is a fundamental event in T-cell immunity and activation, CD3, which is also a component of the TCR complex, is perceived as a specialized hallmark of T-cells (18).

The subjacent importance of CD3 in liver pathology is likely due to the fact that liver is a dominant immunoregulatory organ as well as being an overwhelming origin of immune responses (19). The interconnectivity between liver damage and the progression and return of inflammatory responses is evident in drug-induced liver damage primarily including CD3 positive T-cells (20). Mechanistically, liver damage originates from immunological responses predominantly induced by T-cells, which are tightly associated with immunogenicity and hepatotoxicity (21). With regard to these aspects, there is negligible skepticism that liver damage is mediated by immune responses primarily led by T-cells (22). Previous examinations also found that T lymphocytes, especially CD3+ T cells, appear in the liver after initial liver cell injury and subsequently aggravate hepatocellular damage (23). Conclusively, prior to the copying and exacerbation of liver injury, changes in T-cell populations and function evidently occur as a result of injured accumulated liver (24). Moreover, it was illustrated that changes in CD3 expression levels during hepatotoxicity caused by various agents were intimately associated with the progression of liver injuries (25). From these aspects, fundamental insights into CD3 could contribute to a basic study for the resulting immunoregulatory therapies, targeting a form of defense against progressional drug-induced hepatotoxicity, and elucidating further information regarding essential mechanisms (26).

2. OBJECTIVE

The main objectives of the present study were to explore the modulatory effects of statins, vitamin E, and moringa oleifera extract on CD3 expression in ribociclib-induced hepatotoxicity in rats.

3. MATERIAL AND METHODS

Moringa Olifera preparation

Moringa oleifera leaves (2 kg) were freshly collected from an agricultural site located at Sudat City Menoufia Governorate Egypt (lat 30.3597N, long 30.49520E). The leaves were cleaned with distilled water and dried at room temperature (22 °C) in the open air. Once the leaves dried completely, the were powdered finely (27). The produced powder was soaked in 70% ethanol for 48 hours at 22°C and filtered in a filter paper. The filtrate was then evaporated to dryness to yield a concentrated extract. The extract was autoclaved and stored in a sterile container at 4 °C until it was needed (27). Moringa oleifera extract's phytochemical constituents were characterized in our lab and other studies by using liquid chromatography–mass spectrometry (LC-MS) (27).

Vitamin E

Nature's Life -Vitamin E® was purchased from Nature's Life Company and consists of 70% to cotrienols and 30%a-tocopherol. Supplementation protocol is 30 mg/kg/d of Nature's Life -Vitamin E® by oral gastric tube (28).

Animal model

Fifty male albino rats, aged 9 to 10 weeks, were obtained from the animal house at Jordan University of Science and Technology in Irbid, Jordan. The rats were divided into five groups (N=10), and were given time to acclimate in a well-ventilated room with a 12-hour light/dark cycle. They had unrestricted access to food and water. The study was approved by the Zarqa University Institutional Research Board (approval no. 8023) and was carried out following the guidelines for the care and use of laboratory animals.

Animals were randomly divided into the following groups:

- Group 1: (N=10) rats received 2 mL of normal saline daily, were considered the normal controls.
- Group 2: (N=10) rats were administered 5 mg/kg ribociclib via oral gavage.
- Group 3:(N=10) rats received 5 mg/kg ribociclib with a dose of Statin 200 mg/kg daily.
- Group 4: (N=10) rats were administered 5 mg/kg ribociclib treated with Vitamin E (30 mg/kg) daily by oral gavage.
- Groups 5: (N=10) rats were administered 5 mg/kg ribociclib treated with Moringa Olifera Extract 400 mg/kg orally in a 1-ml olive oil for 42 days (29).

Immunohistochemistry protocols

Liver tissues were prepared in a tissue processor, cut, and sectioned onto charged slides. Then, slices were deparaffinized at 65 °C in an oven for one hour. Afterward, the slides were submerged using a hydrating procedure from xylene to distilled water. The sections were exposed to a solution of 1 % hydrogen peroxide in 100 % methanol for 20 min to reduce or prevent the action of naturally occurring peroxidase. To reduce non-specific binding, the slides were rinsed in phosphate-buffered saline (PBS, pH 7.2 – 7.4) for five minutes before being treated with 1 % bovine serum albumin (BSA) for 30 min. The monoclonal antibody and accompanying immunohistochemistry reagents were allowed to reach 37 °C before use. The monoclonal antibody (CD3, Sakura Company) was diluted 1:100 and then applied on the slides, followed by an hour of incubation in a humid chamber. The slides were washed for five minutes in PBS (PH 7.2 – 7.4) and treated with

secondary biotinylated antibodies for 20 min. After washing for five minutes in PBS (pH 7.2 – 7.4), slides were incubated with streptavidin and horseradish peroxidase for 20 min and washed again with phosphate buffer saline (pH 7.2 - 7.4) for additional five minutes. To evaluate immunohistochemistry reactions, slides were washed via tap water to stop the reaction after being incubated with DAB (3, 3'- diaminobenzidine) until a reaction occurred and a brown residue was produced. Slides were then mounted on a microscope stage after being rinsed with water, dried, and counterstained for 30 seconds with hematoxylin.

Statistical analyses

Statistical analyses were conducted using the Statistical Package for the Social Sciences (IBM, Version 22.0). Data are presented as the mean ± standard error of the mean (SEM). A p-value of ≤ 0.05 was considered statistically significant.

4. RESULTS

The expression of CD3 in the control group

As seen in Figure (1), this micrograph from the liver tissue stained for CD3, T lymphocytes. The staining shows differential staining pattern of small, dark brown-stained cells scattered throughout the hepatic tissue. The normal liver tissue in background is stained lighter (blue) and highlights liver cells and other structures. The structures of the liver are seen to have regular arrangement with clear nuclei that look blue as counterstained. T lymphocytes are seen as small dark-brown spots sprinkled throughout the liver parenchyma. The arrangement of T cells may indicate the infiltration of immune cells. This often signifies inflammation, hepatitis, or an immune response within the liver.

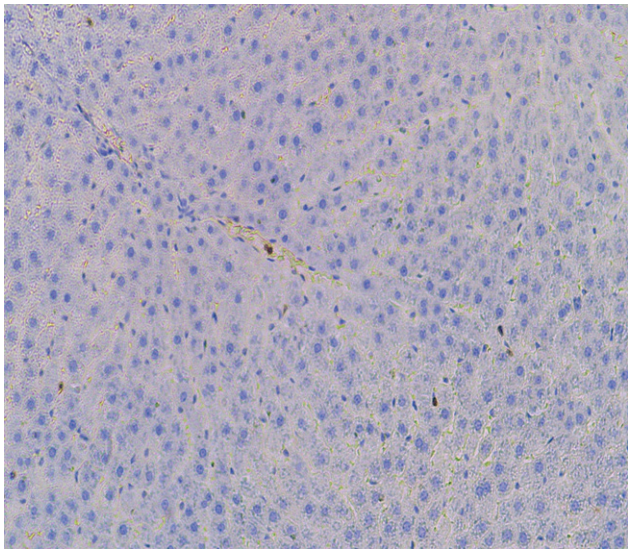

Figure 1. The expression of CD3 in the liver control group

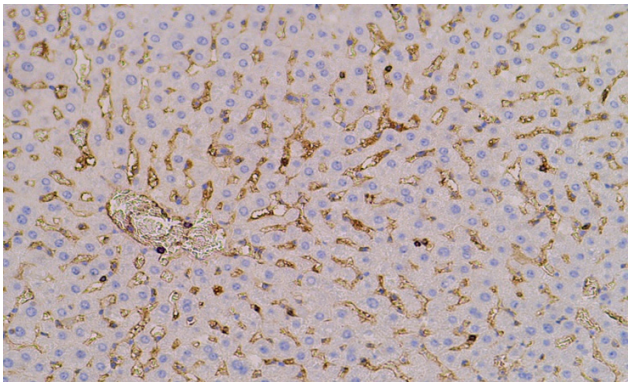

Figure 2. Liver treated with Ribociclib

The expression of CD3 in liver treated with Ribociclib

As shown in Figure (2), the immunohistochemically stain on this liver tissue sample is due to the treatment of Ribociclib. Ribociclib is a medicine that is often used to treat cancer cells that have spread. It may be seen to cause changes in liver hepatocytes and infiltration of inflammatory cells and bile ducts. The brown color is a sign on the IHC that the primary antibody has found its target. As indicated by the marker, the staining appears to be along the membrane of the hepatocytes, the bile ducts, or the endothelial cells. The cells are intact, and the nucleus is stained blue (hematoxylin). There is stain present in structures associated with bile or endothelial components which may be connected with the cytoskeletal or membrane proteins of cells. The arrangement of sinusoids remains distinguishable. The staining of CD3 suggests an immune-mediated hepatic effect or mild hepatotoxicity if there's enhanced immune cell infiltration. From a pathological point of view, it seems that Ribociclib may be causing an inflammatory response.

The expression of CD3 in liver treated with Ribociclib and statin

Figure 3 showed very little brown staining, indicating a small number CD3-positive T cells in the liver parenchyma. The Ribociclib and Statin co-treatment does not strongly induce T-cell infiltration. There are only a few scattered CD3-positive cells, probably residing in the hepatic sinusoids, or near portal tracts. The liver cells are intact, with distinct recognizable nuclei blue. There is no congestion and distortion in sinusoidal spaces architecture. There is no significant clustering of immune cells, suggesting little to no inflammatory response. Statins lower inflammation, thus reducing T-cell entry into the liver. Using both drugs likely keeps the amounts of CD3 positive cells low, suggesting that the combination treatment does not trigger significant T-cell-mediated inflammation in this context.

From a pathological point of view, the low number of CD3 positive cells indicates that T cells are not present in large numbers, suggesting that this liver tissue is not undergoing active immune-mediated inflammation. Since there is a preserved structure of the liver, it would mean that there is not much liver toxicity at this stage. The low incidence of lymphocytic aggregates indicates that this drug combination does not produce significant immune responses in the liver.

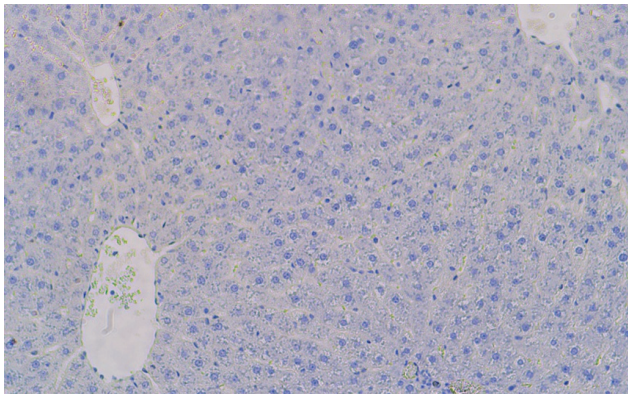

Figure 3. Liver treated with Ribociclib and Statin

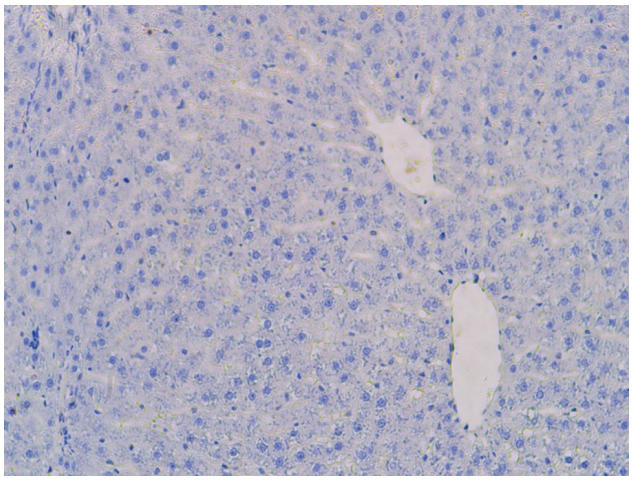

Figure 4. Liver treated with Ribociclib and Moringa Olifera Extract

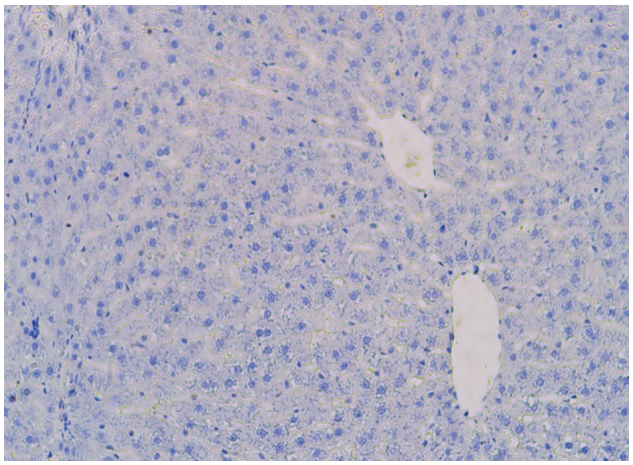

Figure 5. Liver treated with Ribociclib and Vitamin E

Treatment of liver with Ribociclib+ Moringa Olifera Extract

As shown in Figure 4, CD3-positive cells are sparsely distributed in the liver parenchyma. The presence of CD3-positive cells is very low suggesting that there is less infiltration of immune cells compared to an inflammatory liver state. T cells do not cluster together significantly indicating that the treatment does not elicit any strong hepatic immune response. Hepatocytes are well-preserved as indicated by presence of intact nuclei. The sinusoidal spaces are open and unchanged, with no evidence of congestion or architectural distortion. The portal tracts are present but are not infiltrated by any inflammatory cells suggesting no intraportal inflammatory activity. The low level of CD3 staining indicates low levels of hepatic T-cell infiltration, suggesting the combination of Ribociclib and Moringa oleifera extract does not cause excessive immune-mediated inflammation. The liver structure shows no impairment indicating it may not cause much liver damage at this time. The anti-inflammatory property of Moringa oleifera extract may play a role in inhibiting immune cell infiltration that may have counteracted the inflammatory adverse effect of Ribociclib.

The expression of CD3 in the liver treated with Ribociclib and Vitamin E

Figure 5 showed that hepatic parenchyma has scattered CD3 positive cells (T lymphocytes which stain brown). There is a low density of T cells in the liver which indicates there is not much immune-mediated inflammation present. This

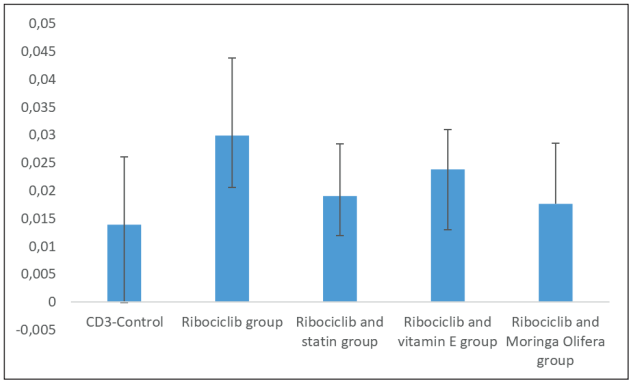

Figure 1. Schematic diagram of the expression of CD3 in the Study groups

Group	Mean	Standard deviation
Control group	0.0139	0.01223
Ribociclib group	0.0299	0.01400
Ribociclib and statin group	0.0191	0.00931
Ribociclib and vitamin E group	0.0239	0.00713
Ribociclib and Moringa Olifera group	0.0176	0.01098

Table 1: The expression level of CD3 in the study groups

Group	Mean	SD	Significance
Control group Ribociclib group	0.0139 0.0299	0.01223 0.01400	0.014
Ribociclib group Ribociclib and statin group Ribociclib and statin group	0.0299 0.0191	0.01400 0.00931	0.058
Ribociclib group Ribociclib and vitamin E group	0.0299 0.0239	0.01400 0.00713	0.246
Ribociclib group Ribociclib and Moringa Olifera group	0.0299 0.0176	0.01400 0.01098	0.043

Table 2: The relationship between study groups (independent T test)

image indicates a weak immune response in the liver compared to untreated or inflammatory conditions. The blue-stained nuclei display normal-looking hepatocytes. Sinusoidal spaces are well opened, well defined without any congestion and structural changes. The presence of immunity cells in the portal tracts suggest that, there isn't much portal inflammation. Ribociclib can inhibit cell growth because it is a CDK4/6 inhibitor might block immunity. Vitamin E might limit the oxidative impacts of ribociclib and also lessen some damage. The combination therapy might have hindered immune cell entry into the liver, probably due to vitamin E's protective effect against oxidative stress or inflammation.

Computational expression of CD3 in the study groups

Table 1 and Figure 1 showed the expression level of CD3 in the study groups. At basal level, the expression of CD3 in the control group was 0.014±0.0122. Treatment with Ribociclib increased the expression level of CD3 (0.0299±0.014). The use of treatments with statin, vitamin E, and Moringa Olifera lowered the expression level of CD3.

The relationship between study groups

Table 2 showed the relationships among study variables. There was a significant relationship between the expression of

CD3 in the control group and Ribociclib group (p=0.014). another significant relationship was shown between Ribociclib group and Ribociclib and Moringa Olifera group (p=0.043).

5. DISCUSSION

Ribociclib is the Novartis drug (market name Kisqali) that is a CDK4/6 inhibitor which slows the growth of cancerous cells (1). It is used for treatment purposes (2). Targeted therapies can cause severe liver toxicity and immune modulation (12, 13). The CDK inhibitors were not intended to target normal tissues but do so inadvertently (30). As a result, normal tissues such as the liver are usually affected (14). Vitamin E is an antioxidant (24). Scientists have been researching vitamin E's ability to protect the liver from drug damage recently (23). Evaluating the CD3 markers of the immune reaction in the liver due to co-administration of Ribociclib and Vitamin E offers meaningful insights (24).

T lymphocytes are able to greatly influence the adaptive immunity and CD3 is a useful marker (12). Positive CD3 reaction in liver tissue shows lymphocyte infiltration in drug-induced drugs (13). If CD3 is less present, there are minimal immune actions, or there is immune suppression at that time (14).

The research found that there was a low level of CD3 + ve T cell infiltration in liver tissue, due to Ribociclib and Vitamin E treatment (no caludering of functional architecture). The treatment is unlikely to cause significant damage to the immune system. The results differ from other CDK4/6 inhibitors like Palbociclib which seem to have immune-modulating properties such as T cell proliferation (31). This means there is low immune damage in the liver tissue with Ribociclib treatment (31). In another study, it has been shown that Ribociclib could have immune suppressive effects. Studies by various researchers in the past who introduced CDK4/6 inhibitors in breast cancer, showed they alter T cell behavior (31).

Vitamin E may prove beneficial in liver diseases as it restrains immune response or activity through limiting oxidative stress and inflammation (32).

Vitamin E is a variety of tocopherols and tocotrienols that have antioxidant and anti-inflammatory effects. It protects cells against serious damage from drugs that damage the liver. Many studies show vitamin E supplementation reduces large infiltration and cytokine production of hepatic T-cells in NAFLD and drug-induced toxicity (33).

The use of chemotherapy helps in decreasing lipid peroxidation and chromosomal damage in liver. It minimizes the signal-generating substances of inflammation in the liver and T-cell recruitment. It stops drugs from stopping the normal functioning of mitochondria and, thus, causes less apoptosis and necrosis (33).

Most treatment groups showed varying levels of CD3 expression for T-lymphocytes. According to table 2, there was a significant difference between the control and Ribociclib groups (p value = 0.014). There was also a significant association with the Ribociclib group as well as the Ribociclib and Moringa oleifera group (p= 0.043. p=0.043). The findings indicated that employing Ribociclib solely or Ribociclib plus Moringa oleifera considerably impacts T-cell dynamics, specifically the control or Ribociclib alone.

Ribociclib inhibits the G1 phase of the cell cycle, which increases the concentration of cancer cells. It inhibits cyclin-dependent kinase 4/6 (CDK4/6) (49). New evidence shows CDK4/6 inhibitors change the immune environment (33). Different studies state that inhibition of CDK4 or 6 causes T-cell modulations, which means either reducing T-regulatory cells or T effector cells, depending on the context (31). Due to the significant difference between CD3 expression in control and Ribociclib groups, we can conclude that the effect of Ribociclib on hepatic tissue can be an immune-modulatory one that can result in T-lymphocytes infiltration from baseline (30).

Moringa oleifera contains various ingredients, including flavonoids and phenolic acids, proven to have anti-inflammatory action, antioxidant action and immunomodulatory action (34). Studies prove that extract of Moringa oleifera can decrease the levels of pro-inflammatory cytokines like TNF-α, and IL-6. And it may modulate the T-cell response (35). The influence of Moringa oleifera on Ribociclib can be observed via the Moringa oleifera group owing to the large difference in the Ribociclib group and the Ribociclib and Moringa oleifera group (35). Ribociclib alone causes T-cells to be more present or more active but Moringa oleifera due to its anti-inflammatory action can lower CD3 expression (35). On the other hand, if Ribociclib inhibits T-lymphocyte infiltration, Moringa oleifera may recover or increase immune cell numbers by maintaining a less inflammatory milieu (33).

6. CONCLUSION

The levels of CD3 were similar in the absence or presence of Ribociclib, and also in Ribociclib and Ribociclib and Moringa oleifera group. Therefore, the inhibition of CDK4/6 can interact with botanicals. To keep immune homeostasis, anti-tumour activity and other functions in balance, understanding these interactions is crucial. Next studies ought to involve judicious investigation of phenotype and functional assays of immune cells and liver function markers to allow a detailed analysis and enhance clinical translation chances.

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