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Candesartan Mitigates Paclitaxel-Induced Peripheral Neuropathy in Human Neuron Cells Lines

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Abstract

Paclitaxel belongs to the initial taxane category. It is employed to treat diverse types of cancers, including ovarian, lung, and breast cancers. Paclitaxel is associated with the highest prevalence of peripheral neuropathy. The detection of paclitaxel-induced peripheral neuropathy (PIPN) may necessitate a reduction in dosage or discontinuation of treatment, which can have consequences for cancer care. Activation of angiotensin type 2 receptor (AT2R) has shown neuroprotective effects in different rodent models. The aim of this study is to assess the potential impact of candesartan in mitigating the deleterious effects of paclitaxel on human neuronal cells.The methods involved immunocytochemistry to validate neurons cells depend on the expression of BIII-tubulin protein. WST-8 test was used on human neuron cell cultures to assess the individual and combined cytotoxicity and inhibitory ratio (IR%) of paclitaxel and candesartan. The Chou-Talalay index(CI) equation was utilized to determine if the interaction was antagonistic, additive, or synergistic. As well as investigate the morphological changes in neuronal axons. Our findings demonstrated a notable expression of the BIII-tubulin protein in neurons cells. The DAB staining showed significant($P<0.05$) than hematoxylin staining in neuron cells culture. Cells viability assessment showed increase in the inhibitory ratio (IR%) when comparing paclitaxel to the control group at all serial concentrations, with statistical significance ($P<0.05$). On the other hand, candesartan did not show any significant difference compared to the control group ($P>0.05$). Interestingly, the combination treatment group showed a significant reduction in the IR% when compared to the paclitaxel group. The estimated Chou-Talalay index (CI) values suggest a significant antagonistic interaction between paclitaxel and candesartan at different dosages in sequential concentrations (CI >1.1). Neurons cells morphology revealed that an enhancement in the neuronal axons outgrowth in the combination (paclitaxel+candesartan) compared to paclitaxel alone. Conclusion candesartan can potentially mitigate the cytotoxic effects of paclitaxel chemotherapy on neuron cell culture.

Keywords: Candesartan, Chou-Talalay index, Inhibitory ratio, Paclitaxel, Peripheral neuropathy.

Introduction

The taxane family comprises a major collection of neurotoxic anticancer medications, with paclitaxel serving as its inaugural member. Paclitaxel is administered for the treatment of various cancer types, including ovarian, lung, and breast malignancies. It is crucial to acknowledge that anticancer therapy is associated with a wide variety of toxicity, and these side effects may impact the health of patients, potentially influencing their medication adherence [1,2]. Paclitaxel has the highest prevalence of peripheral neuropathy and is also linked to the most severe instances of symptoms caused by chemotherapy-induced peripheral neuropathy (CIPN) [3]. Paclitaxel-induced peripheral neuropathy PIPN has a pattern that depends on the length of the nerves and is mostly characterized by unpleasant sensory symptoms, such as abnormal sensations or abnormal sense of touch, especially sensitivity to normally non-painful stimuli [4]. The detection of paclitaxel-induced peripheral neuropathy (PIPN) may necessitate a reduction in dosage or discontinuation of treatment, which can have consequences for cancer care and overall life expectancy. Moreover, the existence of persistent pain linked to CIPN is connected to the emergence of other comorbidities like anxiety, sadness, and insomnia, which can greatly detriment one's overall well-being [5]. Therefore, it is essential to prioritize the prevention and improvement of CIPN with appropriate treatment approaches. It is crucial to avoid the necessity of reducing the dosage or stopping anticancer treatments and to improve the overall quality of life for patients.

Diverse techniques have been utilized to investigate PIPN. These techniques involve

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studying the direct effects of paclitaxel on sensory neurons in the dorsal root ganglia (DRG) of mice and DRG produced from human induce pluripotent stem cells; furthermore, experiments involving live animals and genetic techniques in people have been carried out [6,7].The initial impact of paclitaxel appears to be associated with distinct modifications in the microtubules of sensory neurons. Further modifications have been detected in the control of intracellular calcium ions, axonal transport, mitochondrial function, and the release of neuropeptides [8-12]. The connections between neurons in the peripheral nervous system and nearby cells, including Schwann cells, satellite glial cells, immune cells, and specialized intradermal mechanoreceptor cells like Merkel cells and epidermal keratinocytes, as well as the connections between the central axon of DRG sensory neurons and astrocytes and microglia, could potentially contribute to the progression of the disease [13, 14]. Various preclinical studies have demonstrated that renin-angiotensin system (RAS) inhibitors, such as angiotensin receptor blockers (ARBs) and angiotensin-converting enzyme inhibitors (ACEIs), exhibit neuroprotective properties in different animal models of peripheral neuropathy, including those produced by trauma, diabetes, and toxins [15-19].

Candesartan is an antihypertensive medication that belongs to the class of ARBs; and, it blocks the angiotensin type 1 receptor (AT1R), resulting in the heightened stimulation of the angiotensin type 2 receptor (AT2R) by angiotensin II (AngII); furthermore, activation of AT2R has shown neuroprotective benefits in different rodent models of traumatic brain injury and ischemic stroke [20-22].

The primary goal of this study is to assess the potential impact of candesartan in mitigating the deleterious effects of paclitaxel on human neuronal cell lines.

Material and method

Drugs and cell culture

Paclitaxel and candesartan are sourced from Santa Cruz Biotechnology, USA.dimetyl sulfoxid (DMSO), a solvent obtained from Sigma Aldrich in St. Louis, MO, USA, was utilized to dissolve paclitaxel. The neuron cell was obtained from a biotechnology laboratory. That is located in Baghdad, Iraq.

Media preparation

Media was prepared by mixing the minimum essential medium (MEM) liquid sourced from Elabscience, china with antibiotic–antimitotic solution sourced from Capricorn Germany then 10ml of puffer 4-(2-hydroxyethyl) piperazineethanesulfonic acid (HEPES) buffer solution sourced from Elabscience, China was added to maintain pH between 6.8 -7.2 in double distal water then the media was filtered with Nalgene filter sourced from Capricorn Germany 0.22 Mm pore size to sterile the media [23].

Maintenance of cell culture

Cell cultures were maintained in Roswell Park Memorial Institute (RPMI) sourced from Capricorn Germany supplemented with 10% Fetal bovine supplied by Elabscience China, 100 units/mL penicillin, and 100 µg/mL streptomycin sourced from Capricorn, Germany. Cells were passaged using Trypsin-EDTA(ethylene diamine tetraacetic acid) sourced from Capricorn Germany reseeded at 50% confluence twice a week, and incubated at 37 °C [23].

Immunocytochemistry of β tubulin III

Before conducting the immunocytochemistry ICC test, which seeks to identify and classify neuron cells using BIII- tubulin as a specific marker for neuron cell, we placed 100 ml of cell solution into each well of 8 charged slides. To separate the cells from the monolayer and form a suspension of individual cells, 3 ml of Trypsin-EDTA was added to the cell culture flask obtained from SPL Life Science Korea and let work for 3 minutes. After that 5 ml of fetal bovine serum FBS was added to counteract the effects of the other medium [24].

Sample staining and imaging

After hydrating and dewaxing the paraffin component, individual cells were incubated with a 3% H2O2 solution for 10 minutes. Normal Goat Blocking Buffer obtained from Elabscience, USA, was then added and the mixture was incubated at 37°C for 30 minutes. After that, the BIII- tubulin primary antibody obtained from Santa Cruz, USA, was applied and incubated at a temperature range of 20 to 37°C for 1 to 2 hours. After the incubation period, the sample was warmed again at 37°C for 30 minutes. A Polyperoxidase-anti-Mouse/Rabbit IgG sourced from Elabscience, China, was introduced and the mixture was incubated for 20 minutes at either 37°C or room temperature. Two to three rinses with phosphate-buffered saline (PBS) sourced from Elabscience, China, were conducted. One drop (about 50µL) of DAB Concentrate was mixed with every 1 mL of DAB Substrate to create the DAB working solution. The mixture was thoroughly mixed, and the time it took for the DAB color to appear was carefully monitored. A tawny or orange hue indicated a positive outcome. Deionized water was applied to rinse the area to stop the chromogenic process. Following the acquisition of an image of the cell culture using an Olympus microscope, the optical density of the positive DAB staining and negative control groups were quantified using Image J software. The obtained data were further analyzed using Graph Prism software [24].

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Cytotoxicity assay

The experiment involved growing cells into four different groups: a control group, a group treated with candesartan, a group treated with paclitaxel, and a group treated with a combination of paclitaxel and candesartan. To determine the inhibition ratio of taxol, candesartan, and their combination on neuron cell culture, serial dilutions of paclitaxel, candesartan, and combination were applied at varying concentrations (1000, 500, 250, 125, 62.5, 31.2 Mg/ml). The cell viability was evaluated after three days of incubation. Following the removal of the medium, 10µL of CCK-8 Buffer (WST-8) sourced from Elabscience, USA was added to each well and left to incubate for one to four hours. The incubation conditions for CCK-8 were identical to those used for cell culture. The optical density (OD) value was then determined using a microplate reader at a wavelength of 450 nm.

The cell survival rate was calculated using the formula:

$$\textbf{Cell Survival Rate}\% = (\textbf{OD sample} - \textbf{OD blank}) \div (\textbf{OD control} - \textbf{OD blank}) \times 100\% \quad \textbf{(1)}$$

The inhibition rate was calculated using the formula:

$$\textbf{Inhibition Rate}(\%) = (\textbf{OD control} - \textbf{OD sample}) \div (\textbf{OD control} - \textbf{OD blank}) \times 100\% \quad \textbf{(2)}$$

Lastly, a light microscope was used to examine the cells [25].

Chou–Talalay Analysis

The effective dose 50 (ED50) values were determined for each drug used in the cell culture. The study employed a variable ratio strategy to examine the opposing effects of paclitaxel and candesartan. The Chou-Talalay combination indices (CI) were computed using CompuSyn software sourced from Combo Syn, Inc., Paramus, NJ, USA to assess the interaction relationship between paclitaxel and candesartan. The confidence intervals were calculated using separate equations that were non-overlapping and ratios of candesartan and paclitaxel that were variable; where, CI value is defined as additive when it falls within the range of 0.9 to 1.1; while the synergism relationship is defined when the CI value is below 0.9; and finally, the antagonism relationship is denoted when the CI value is over 1.1 [26].

Statistical analysis

The data of the current study were presented as means±SEM. A one-way ANOVA analysis of variance was used to compare data between treatment groups. Data, collected from three timed cycles of the experiment, were considered statistically significant at $P < 0.05$. A Graph Pad Prism 6 software was used for the analysis which was sourced from Graph Pad Software, Inc. San Diego, California.

Results

Characterization of neuron cells by ICC of β tubulin III protein

The expression of β-tubulin III was observed in the positive control cell, indicated by the brown color resulting from DAB antibody staining, as shown in Figure 1B. In contrast, the negative control in Figure 1A showed a blue color due to hematoxylin staining. Furthermore, there were notable differences in the OD of DAB between the positive control PC and negative control NC, as depicted in Figure 1C. The expression of β-tubulin III is a crucial process to ensure the survival and specificity of human neuron cells in culture conditions during the differentiation of neuron cells.

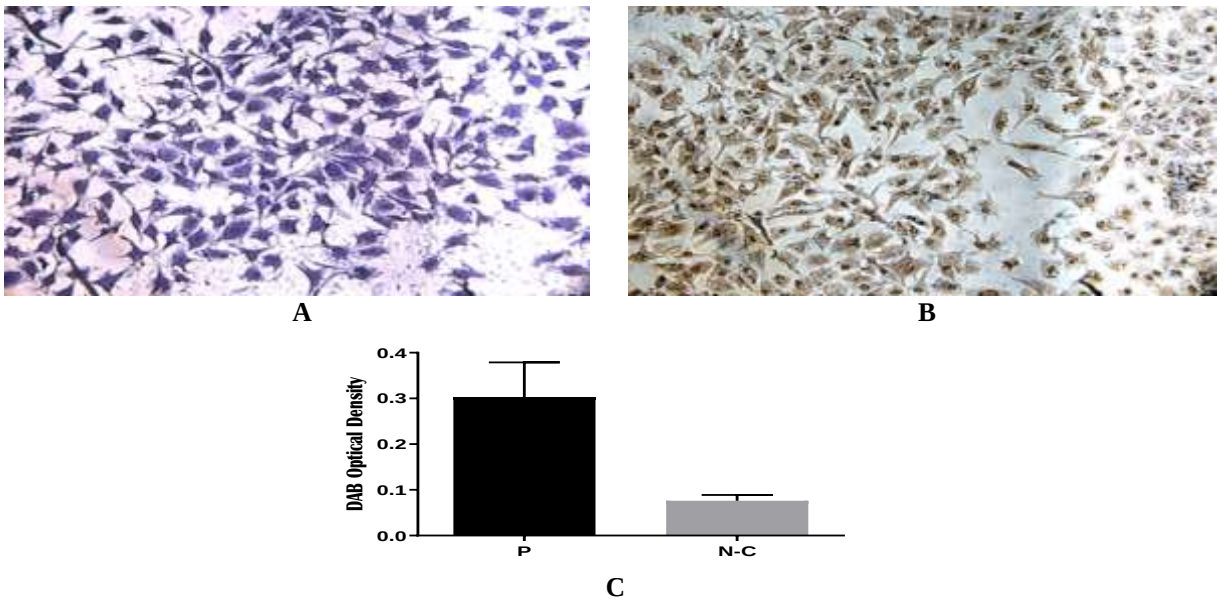

Figure 1. Immunocytochemistry assay of neuron cells to characterize β tubulin III protein. (A) hematoxylin stain (blue color) negative control. (B) DAB primary antibody β tubulin III (brown color). (C) DAB optical density between positive control and negative control.

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Cytotoxicity and inhibitory ratio (IR%) of paclitaxel and candesartan

Figures 2A and 2B showed that the paclitaxel group displayed a significant inhibition ratio IR% in all serial concentrations compared to the control group. This difference was statistically significant, with a P value of less than 0.05. The IR% was determined to be 77.2% at a 1000 mg/ml concentration.

Furthermore, it was noted that the toxicity of paclitaxel diminished as the concentration dropped. Nevertheless, it exhibited cytotoxicity even at a minimal concentration and was notably distinct from the control group(P value < 0.05).

In the group receiving candesartan, the inhibition ratio (IR%) was 27%; and, the P value was not statistically-significant (P value >0.05) when comparing all serial concentrations to the control group as depicted in Figures 2C and 2D.

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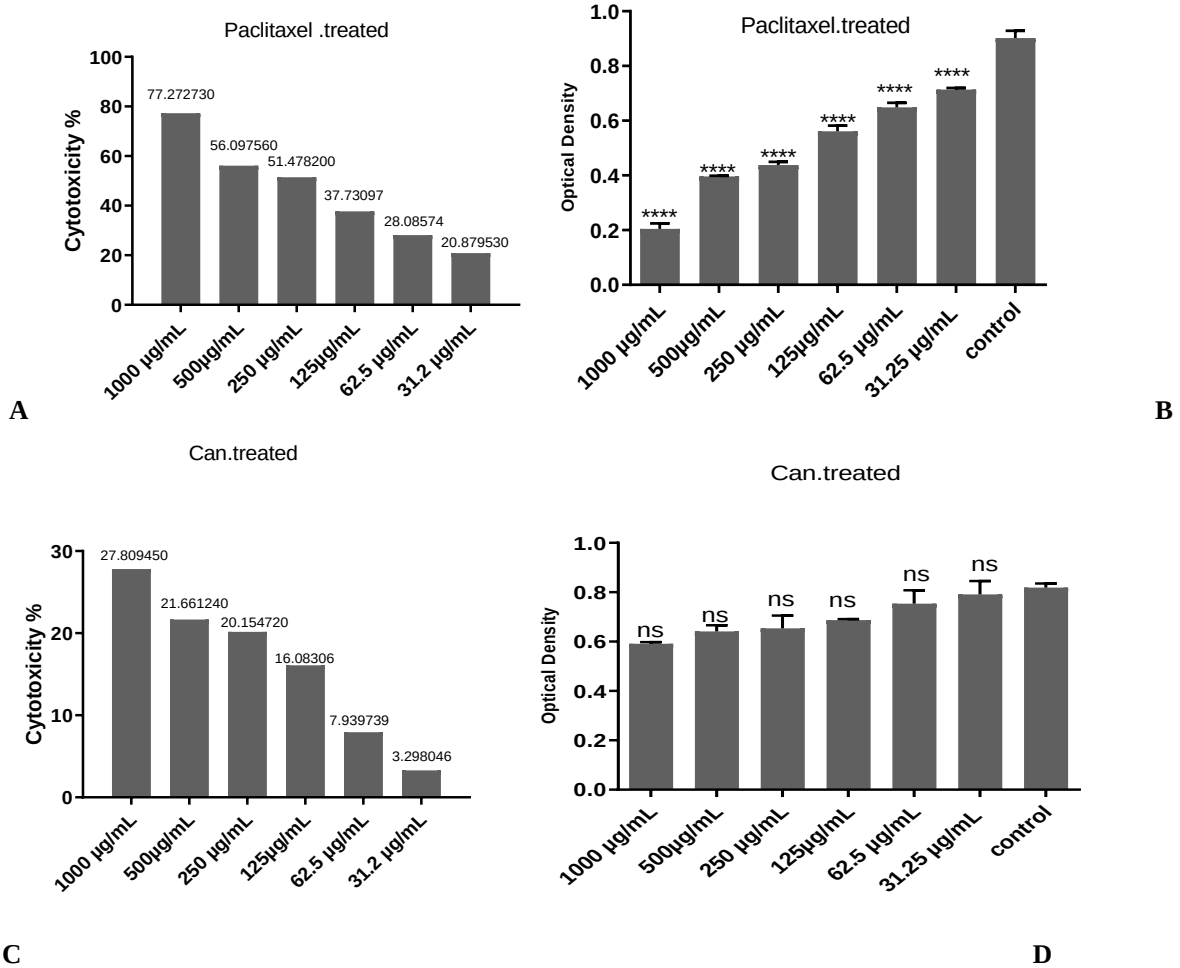

Figure 2. Assessment of cytotoxicity and the inhibitory ratio IR for the paclitaxel and candesartan alone on neuron cells in vitro by using the WST-8 assay test. (A) Cytotoxicity of paclitaxel IR% was 77.2 at highest concentrations (1000Mg per ml). (B) OD of the paclitaxel-treated cell. All concentrations had significant changes with the control group(P<0.05). (C) cytotoxicity of candesartan treated cell. (D) OD of candesartan-treated cells no significant change with the control group (P>0.05).

Figures 3A and 3B showed the inhibitory ratio IR% of the combination chemotherapy paclitaxel and candesartan in different serial concentrations; where, the IR% of the combination-treated cells was 29.8 at 1000Mg/ml, while IR% was 8.1 at the lowest concentration of 31.2Mg/ml; interestingly, IR% was reduced in the combination-treated group compared to paclitaxel alone (Figure 2A). However, the OD of the combination-treated group was statistically-significant compared to that of the control group, as demonstrated in Figure 3B.

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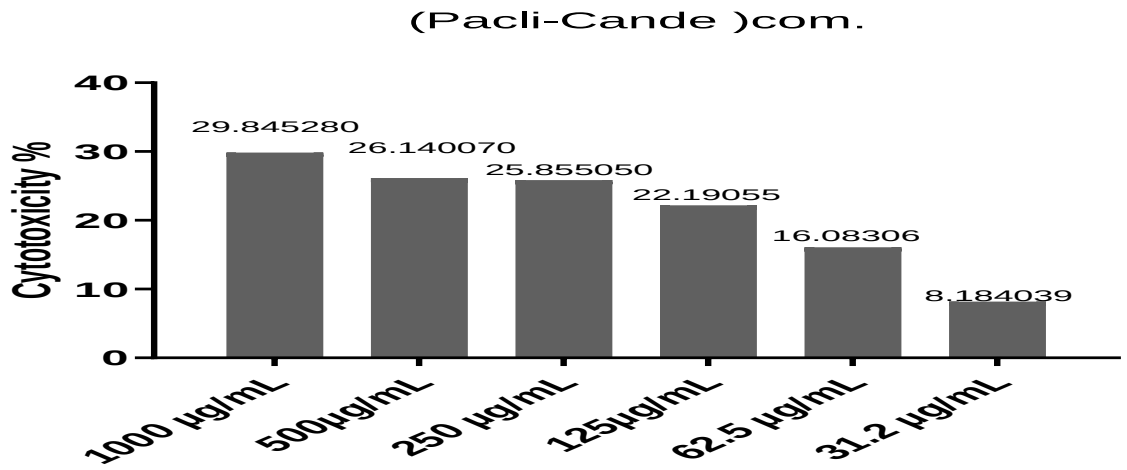

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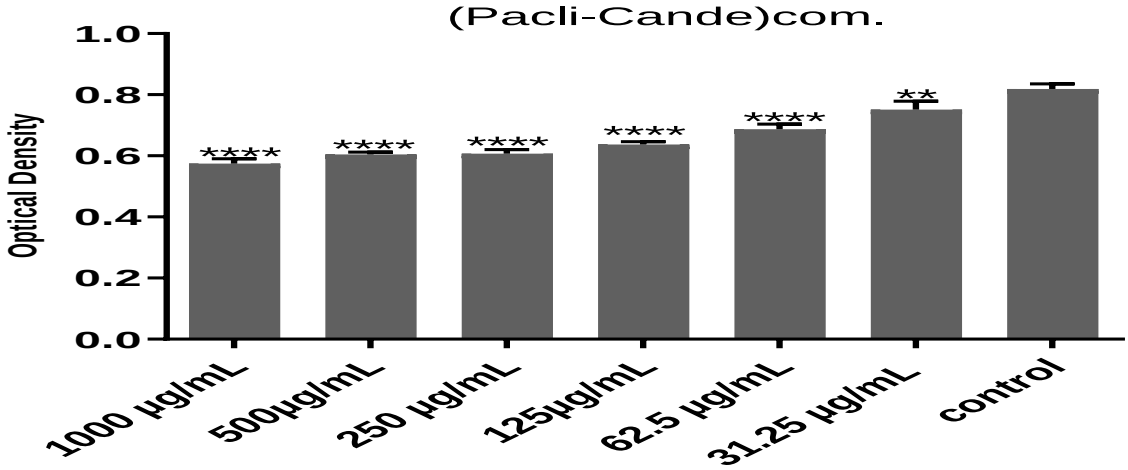

B

Figure 3. Assessment of cytotoxicity and inhibitory ratio IR% of combination chemotherapy paclitaxel+ candesartan. (A) cytotoxicity of combination paclitaxel+candesartan. IR% was 29.8 at highest concentrations (1000Mg per ml). (B) the optical density of combination-treated cells vs the control group.

Chou–Talalay an analysis of the combination-treated cells

The interaction between paclitaxel and candesartan would affect the potential cytotoxic effects of the chemotherapeutic drug (paclitaxel) by the utilization of the Chou-Talalay equation and examined whether candesartan would have an antagonistic, additive, or synergistic effect with paclitaxel. Table 1 shows that the CI was greater than 1.1 for all concentrations, indicating a strong antagonism between paclitaxel and candesartan. The highest CI was 15.4 at 1000mg/ml and the lowest was 2.9 at 62.5.2mg/ml. Figure 4A did not show any point within the triangle or in the border zone due to the highly antagonistic nature of the interaction between Taxol and candesartan. Figure 4B represents the dose-effective curve between paclitaxel, candesartan, and the combination-treated group. Overall, all doses showed reduced cytotoxicity of paclitaxel on neuronal cells.

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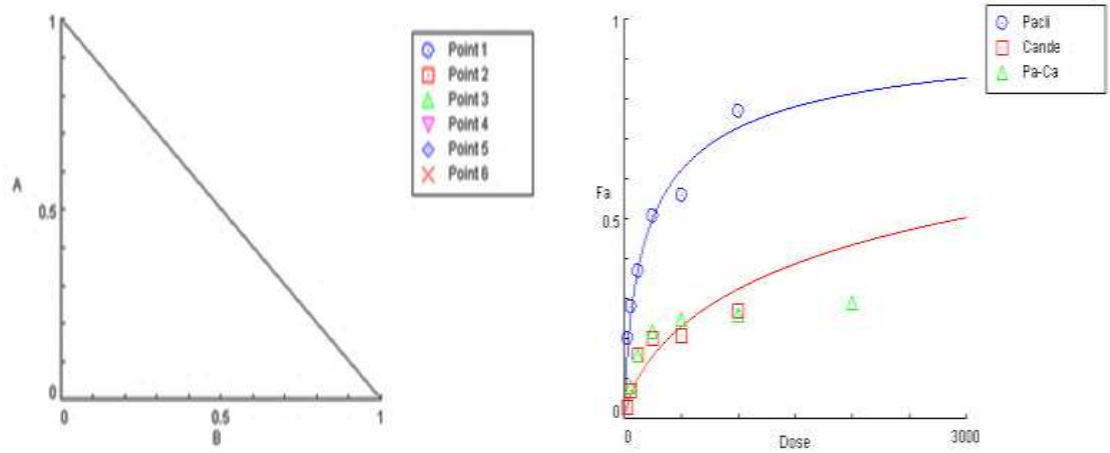


A **B**

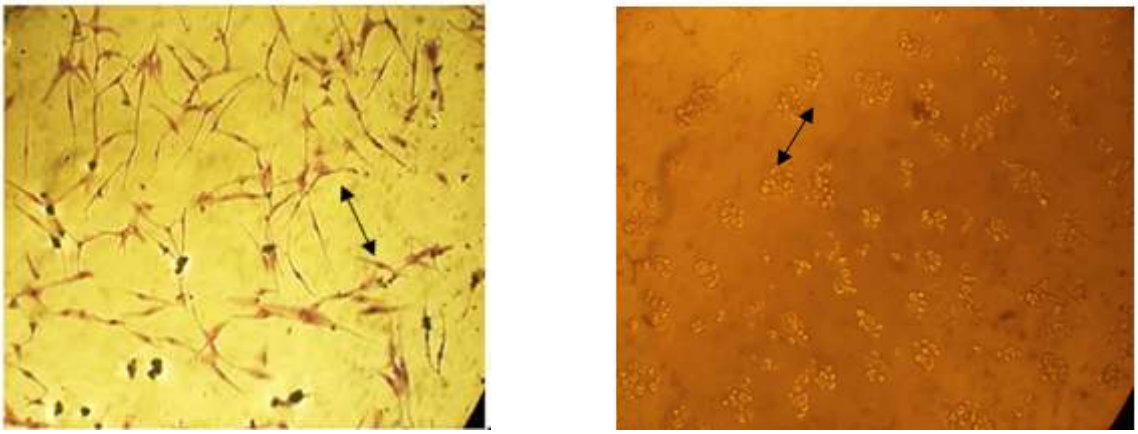
Figure 4. Isobologram analysis of the combination of paclitaxel and candesartan at different concentrations. (A) triangle represents the interaction between paclitaxel and Candesartan. (B) dose- effective curve of paclitaxel, candesartan, and combination.

Table 1. Show the chou-Talalay indices CI. paclitaxel and candesartan were added serial dilution in the same concentration to calculate the CI value using the CompuSyn software program.

Dose paclitaxel Mg/ml	Dose candesartan Mg/ml	Effect	CI
1000.0	1000.0	0.29	15.8476
500.0	500.0	0.26	9.81805
250.0	250.0	0.25	5.29104
125.0	125.0	0.22	3.35574
62.5	62.5	0.16	2.93401
31.2	31.2	0.08	4.47269

Morphology of neuron cells before and after treatment

In Figure. 5, we can see that paclitaxel treatment causes cytopathic damage, which results in axon degeneration in all neuron cells (Figure 5B) compared to the control group (Figure 5A). On the other hand, the group treated with candesartan showed a clear morphology of the neuron axon and cell body, as seen in Figure 5C. Interestingly, the combination of these treatments results in an improvement in the morphology of neuronal axons, as shown in Figure 5D.



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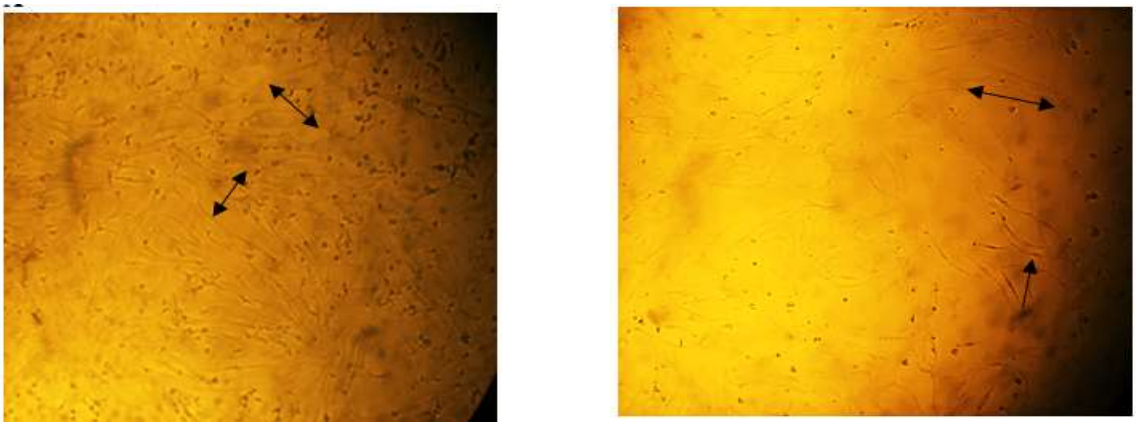

C D

Figure 5. Cytopathic effect of paclitaxel and candesartan alone or / and in combination. (A) Control cell group. The axons of neurons were observed clearly (black arrow). (B) Paclitaxel-treated cells. Cytopathic was observed clearly after 72 hours by axon degeneration (black arrow). (C) Candesartan treated cells. Intact axon and cell body. (D) A combination of treated cells, paclitaxel and candesartan (cell axon), was a clear and elongated (black arrow). Magnification: 400×

Discussion

The main findings of this study suggest that the assessment of the maturity of sensory neuron cells before evaluating the cytotoxicity of different drugs through in vitro research is dependent on the characterization of human neuron cells utilizing BIII- tubulin. Candesartan possesses the capacity to reduce the inhibitory rate percentage of PINP in human neuron cells; moreover, such drug enhances axons' regeneration and growth, hence improving neuron cell degeneration. (Figure 3A and 3B,and Figure 5 D).

The present study shows cases of a significant manifestation of BIII- tubulin in cultivated cells, as illustrated in Figure 1B, where the primary antibody is observed in a brown hue. Besides, the Figure 1A depicts the negative control, which is seen with a hematoxylin stain and appears as a blue tint. In addition, the DAB optical density shows a significant statistical difference (P value <0.05) between the positive control and negative control groups, as shown in Figure 1C. Furthermore, before assessing cytotoxicity during this stage, it is imperative to accurately-classify cultured cells as fully mature neuron cells; and, such classification ensures the reliability of subsequent analyses. Specifically, mature sensory neurons exhibit intricate networks of neurites emanating from their soma; and. this morphological feature is elucidated through the immunolabeling of microtubules with a neuron-specific β tubulin III antibody. [27].

According to the cytotoxicity investigation, this study noticed that the cell inhibition rate (IR%) increased as the concentration of paclitaxel increased; and, the maximum incidence rate percentage (IR%) observed was 77.2% when administered at a dosage of 1000 Mg/ml while the minimum IR% was 20.8% at a concentration of 31.2 Mg/ml. The results are illustrated in Figures 2A and 2B and this finding aligns with another study that asserts the neuropathic damage and anti-cancer effectiveness of paclitaxel are contingent upon the specific dosage and duration of treatment [28]. Additionally, a separate investigation showcased the influence of paclitaxel on human neuron cells, uncovering that the deterioration of the neurons displayed changes that relied on both the amount and length of time of exposure to concentrations typically seen after injection in individuals [29].

The group administered with candesartan did not demonstrate any statistically-significant alterations (P value > 0.05) in neuron cell activity when compared to the control group, as indicated by Figures 2C and 2D; and, the highest concentration of candesartan, 1000 mg/ml, led to an inhibition rate IR% of 27. The collected data provide proof of the safety and positive impact of candesartan as a neuroprotective drug in different neuropathological conditions, as indicated by many research [10,11,13].

The results of this study demonstrated that the concurrent administration of paclitaxel and candesartan led to a substantial reduction in the IR% from 77.7 (figure 2A) when paclitaxel was administered alone to 29.8 in the combination treatment; and, the decrease in IR% was detected at the levels shown in Figures 3A and 3B, and it remained statistically-significant compared to the control group (P value < 0.05). These findings indicate that candesartan may reduce, but not entirely-prevent, PINP. Moreover, the CI value indicated a substantial antagonistic impact between candesartan and paclitaxel was, at all serial concentrations, higher than 1.1, as shown in Table 1. The isobologram (Figure 4A) clearly-illustrated that there were no points of serial dilution in the synergistic or additive zone between paclitaxel and candesartan. In addition, the current investigation included further analysis to investigate the dose-response curve (Figure 4B) for paclitaxel, candesartan, and the

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combined administration of paclitaxel and candesartan. The findings demonstrated a significant decrease in the toxic effects of paclitaxel on neuronal cells when combined with candesartan, in comparison to paclitaxel delivered alone. This discovery aligns with recent research that showcases the neuroprotective effect of candesartan on peripheral neuropathy produced by VCR[30].

Several *in vitro* studies demonstrate that AT2R stimulation by the AT1R blocking agent or Ang II may have a neuroregeneration impact on degenerating neurons. A recent *in vitro* study investigated the effect of the AT2R agonist (CGP42112A) and Ang II, in human neuroblastoma cell line SH-SY5Y, on the differentiation and outgrowth of human neurons, demonstrated that AT2R agonist or Ang II can remarkably-increase the neurite outgrowth. while the treated neuronal cells in the same study, with selective AT2R antagonist (PD123319) showed a significant reduction in differentiation and neurite outgrowth in neuron cell lines [31]. Another in vitro study demonstrated that neurite outgrowth was significantly-increased when NG108-15 cell lines were treated with novel non-peptide agent C21/ M024 (Ang II agonist). On the other hand, an Ang II antagonist (C38/M132) or AT2R antagonist (PD123319) significantly- inhibits neurite outgrowth[32]. Furthermore, AT2R can promote the process of neuronal differentiation produced by neuronal growth factors inhibit the proliferation caused by growth factors, and facilitate growth arrest, which is an important step in proliferation. In the PC12W cell line, Ang II stimulates AT2R leading to a significant increase in the differentiation and neurite outgrowth of neuron cells [33].

This study focused on analyzing alterations in the structure of neurites as a reliable measure of neurotoxicity in chemotherapy-induced neuropathy. Figures 5A and 5B unambiguously illustrated the separate deterioration of axons and conspicuous variations in cytopathic morphology between the control group and the group subjected to paclitaxel treatment. Various approaches were utilized to determine the association between the mechanism of action of paclitaxel and neuropathic damage.The initial effects of paclitaxel appear to arise from distinct modifications in the microtubules of sensory neurons, potentially leading to the degeneration of axons and the death of neurons through necrosis and apoptosis; and, the extent of these impacts is contingent upon the length and intensity of paclitaxel exposure [10,13]. The group administered with candesartan (Figure 5C) demonstrated little changes in morphology and neurite outgrowth in comparison to the control group. Furthermore, this group exhibited a more prominent increase in axon elongation compared to the group receiving paclitaxel treatment. The cells subjected to the combination treatment demonstrate a significant enhancement in axon elongation and neurite formation, as illustrated in Figure 5D. The results are align with that of previous research that demonstrated the ability of candesartan to enhance neuron regeneration and mitigate neuron degeneration via promoting AT2R [17, 34, 35].

Conclusion

Candesartan has neuroprotection and neuroregeneration effects and exhibits the potential to mitigate the cytotoxic effects of paclitaxel chemotherapy, suggesting its role in protecting and treating paclitaxel-induced peripheral neuropathy.

Recommendation for future work

This research seeks to ascertain the viability of candesartan as a prospective therapeutic agent for future applications. Also, we recommend further preclinical and clinical studies as candesartan is a promising therapeutic molecule to repurpose in chemotherapy-induced peripheral neuropathy.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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Ethics Statements

The authors declare that the research does not need to ethics statement as no animal or human is included in this study.

Author Contribution

The authors confirm their contribution to the paper as follows. Karar H. Alfarttoosi: contributed to: study conception and design; data collection; and draft manuscript preparation. Ihsan S. Rabeea: contributed to draft manuscript preparation; supervision. All authors reviewed the results and approved the final version of the manuscript.

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كانديسارتان يخفف من الاعتلال العصبي المحيطي الناجم عن الباكليتاكسيل في الخلايا العصبية البشرية في الأوساط الزرعية

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الخلاصة

ينتمي الباكليتاكسيل إلى فئة الـ تاكسانات الأولية ويستخدم لعلاج مجموعة متنوعة من أنواع السرطانات، بما في ذلك سرطان المبيض والرئة والثدي. يرتبط الباكليتاكسيل بأعلى انتشار لحالات اعتلال الأعصاب الطرفية. قد يستدعي اكتشاف متلازمة الأعصاب الطرفية تخفيض جرعة الدواء أو توقف العلاج، مما يمكن أن يكون له عواقب على الرعاية السرطانية. أظهر تفعيل AT2R تأثيرات عصبية واقية في نماذج الفئران المختلفة. تهدف هذه الدراسة إلى تقييم التأثير المحتمل لكانديسارتان في التخفيف من التأثيرات الضارة للباكليتاكسيل على الخلايا العصبية البشرية. الطرق المستخدمة في إجراء تحليل النسيج المناعي لتوصيف الخلايا العصبية تعتمد على تعبير بروتين البيتا توبولين III. تم استخدام اختبار WST-8 على الخلايا العصبية البشرية لتقييم السمية الفردية والمشتركة ونسبة التثبيط (IR٪) لـ باكليتاكسيل وكانديسارتان. تم استخدام معادلة مؤشر شو تالالاي لتحديد ما إذا كان التفاعل مضادًا أو مضافًا أو تعاونيًا. بالإضافة إلى ذلك، تم استكشاف التغيرات المورفولوجية. أظهرت النتائج زيادة ملحوظة في نسبة التثبيط (IR٪) عند مقارنة الباكليتاكسيل بالمجموعة الضابطة في جميع التراكيز المتسلسلة، بدلالة إحصائية ($P<0.05$) من ناحية أخرى، لم يظهر كانديسارتان أي فرق ملحوظ مقارنة بالمجموعة الضابطة ($P>0.05$). ولوحظ أن مجموعة العلاج المشترك أظهرت تقليلًا ملحوظًا في نسبة التثبيط (IR٪) عند مقارنتها بمجموعة الباكليتاكسيل. تشير قيم مؤشر شو تالالاي المقدرة إلى تفاعل مضاد ملحوظ بين الـ باكليتاكسيل وكانديسارتان في جرعات مختلفة في تراكيز متسلسلة (CI> 1.1). كشف تصوير المورفولوجيا للخلايا العصبية عن تحسين في المورفولوجيا الخلوية العصبية عند استخدام مزيج من الباكليتاكسيل وكانديسارتان. في الختام، يمكن لكانديسارتان بشكل محتمل التخفيف من التأثيرات السامة الباكليتاكسيل كعلاج كيميائي للامراض السرطانية.

الكلمات المفتاحية: كانديسارتان، مؤشر جووي-تلايلي، نسبة تثبيط الخلايا، باكليتاكسيل، الاعتلال العصبي المحيطي.