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Comparative Effects of Isolated ß-Caryophyllene and Duloxetine on Hematological Parameters in Oxaliplatin Induced Anemic Wistar Rats

Onwuka K. C. [1*]
[1]Department of Physiology, Faculty of Basic Medical Sciences, Abia State University.
[*]Corresponding Author Email: onwuka.kelechi@abiastateuniversity.edu.ng

ABSTRACT
Oxaliplatin, an antineoplastic drug that offers a financial burden for patients coupled with an induced peripheral neuropathy, also presents an hematologic deficits such as anemia and neutropenia. However, researches have been ongoing for a cheaper and easily available natural substitute without incidence of pancytopenia. This study investigated the hematologic effects of beta-caryophyllene (BCP) fraction from *Piper guineense* in Wistar rats during oxaliplatin therapy. The rats used in this study were grouped into 5 groups (n=8). Except for normal control, all animals were treated with Oxaliplatin 4 mg/kg of body weight (b.w). Apart from the Negative control, rats were treated daily with Duloxetine 10 mg/kg b.w (control 3), BCP 25 mg/kg b.w (Group 4) and BCP at 50 mg/kg b.w(group 5). After three weeks of administration, the rats were analyzed for hematological parameters ($P<0.05$). There were significant ($P<0.05$) decrease in red cell, hematocrit and white blood cell counts compared to BCP and duloxetine treated groups. However, there was no significant decrease in Platelet counts of group treated with oxaliplatin when compared to those treated with BCP and duloxetine. Oxaliplatin exerts anemic and leucopenic effects which could be ameliorated by BCP ad duloxetine. However, it is possible that it doesn't cause thrombocytopenia in a sub-acute duration (21 weeks). Beta caryophyllene could offer erythropoietic effect in oxaliplatin therapy. The thrombocytopenia seen in clinical co-treatment of oxaliplatin with other drugs may not be a function of oxaliplatin.

Keywords:
Oxaliplatin; Beta-Caryophyllene, Anemia, Neutropenia, Thrombocytopenia.

INTRODUCTION

Peripheral neuropathy is a side effect that is usually associated with antineoplastic drug therapy as sommonly seen in oxaliplatin therapy. Oxaliplatin is mainly used for the treatment of solid tumor Gastrointestinal colorectal cancer (Kuang, *et al.,* 2025; Devanabanda and Kasi, 2023; Zajaczkowska *et al*., 2019; Gou, *et al*., 2018). Oxaliplatin causes damage to the peripheral nerves leading to symptoms such as hyperalgesia, tingling, numbness in the extremities and impairment of motor functions (Jiang, *et al*., 2025; Al Moundhri *et al*., 2015).
Oxaliplatin therapy causes dose dependent myelosuppressions which manifest as decreases in more than one blood cell lines (white blood cells WBC, red blood cells, RBC and platelets) (Devanabanda and Kasi, 2023; Santodiriocco, *et al*., 2008; Cassidy and Misset, 2002). For white blood cells, it causes neutropenia as observed in clinical therapy (Cassidy and Misset, 2002). More evidently among its effect on red blood cells is the serious anemic effect documented as reductions in RBC count, hemoglobin and hematocrit in both preclinical animal study (Lees, *et al*., 2020) and clinical human therapy (Devanabanda and Kasi, 2023). There was also notable increases in mean corpuscular volume, MCV, in some cases of animals studies (Lees, *et al*., 2020) which calls for the constant monitoring of patient on oxaliplatin therapy using full blood count routines (Cassidy and Misset, 2002; Devanabanda and Kasi, 2023). Oxaliplatin also caused thrombocytopenia in clinical cases during the earlier days of oxaliplatin co-therapy (Cassidy and Misset, 2002; Devanabanda and Kasi, 2023). This suppression can lead to changes in haematological parameters such as a decrease in the red blood cells (anemia) white blood cells (leukopenia) and platelets (thrombocytopenia) which play significant role in inflammation (Sabiu, *et al*., 2025). These changes can result to symptoms like fatigue, increased susceptibility to infections and an increased risk of bleeding.
Beta-caryophyllene (BCP) is a natural bicyclic sesquiterpene found in many essential oils, including those derived from cannabis and black pepper.

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It has gained attention for its potential therapeutic effects, including anti-inflammatory, analgesic, and neuroprotective properties. (Benyamin *et al*., 2017). It has shown to be effective as a nociceptive agent (Alberti *et al*., 2020), anti-inflammatory and antioxidative in several experimental models of colitis (Zhang, *et al*., 2017), hypoxia (Liu, *et al*., 2015; Taejoon, *et al.,* 2020), arthritiic rat neurotoxicity (Salles, *et al*, 2020) and brain injury (Vijayakumar, *et al*., 2020). Majority of its action has been linked to its activation of CB (cannabinoid) 2 receptors of the endocannobinoid system (Gertsch, *et al*., 2008; Russo, *et al*., 2011; Klauke, *et al*., 2014). BCP is one of the most abundant phytochemicals in *Piper guineense* which has used as a culinary agent especially in nigerian dishes (Jirovetz, *et al.,* 2002; Ogunwande, *et al*.,2013).

The cost of chemotherapy using oxaliplatin together with the management of its serious adverse effects such as neuropathy ranges averagely between $15,000 to $73,000 in mono/Adjuvant six (6) cycles regimen to years of administrations and management (Shiroiwa, *et al*., 2012; Aballea, *et al*., 2007). In Nigeria, a 12 dose administration coupled with clinical monitoring and services cost about N510,000 to N2,088,600 by computation. This is grossly expensive and unobtainable by most people especially in countries like Nigeria. All these hematological effects manifest as increased infection risk (due to neutropenia), fatigue, pallor, dyspnea (due to anemia) and increase bleeding or easiness to bruising (due to theombocytopenia). However, *Piper guineense*, which has abundance of beta-caryophyllene, is easily available at the Nigerian market. The hematological benefits, together with other benefits beta-caryophyllene may render could point it worthy of gross innovative investments as alternatives for management of adverse effects of oxaliplatin therapy or even replace oxaliplatin therapy for low income earners, since BCP has shown anti-cancer activity even against colon and pancreatic cancer lines (Francomano, *et al.,* 2019). Studies on effect of oxaliplatin therapy on hematological parameters are still limited especially in regards to its neuropathic dose as against analgesic. The aim of the study was to investigate the effect of beta-caryophyllene fractionated from *Piper guineense*, and Duloxetinee on haematological parameters in Wistar rats during oxaliplatin therapy.

MATERIALS AND METHODS

Purchase of Rats and *Piper Guineense* Fruits

Forty Wistar rats (200 ± 10g) and 20 wistar rats (150 ± 20g) was purchased and used for the experimental and acute toxicity studies respectively. Their acclimatization period was for 14 days before the commencement of the study. *Piper guineense* fruits were bought from a dealer in Okigwe market, Okigwe, Imo State. It was authenticated at the Department of Plant science and Biotechnology, Abia State University, Uturu. A sample of it was kept in the herbarium for reference purposes. The Herbarium Voucher number is ABSU/FBS/60.

Extraction of the Essential Oil from *Piper Guineense* Fruits

The method according to Liu *et al* (2018) was used. They were dried using Heating Oven (model: DHG-9053A) and slightly grounded with high speed grinder (Rico MG1803) at a reduced temperature. They were then sieved at particle size of about 425 µm to obtained fine powder (sieve mesh 40; JVAB: jmg-gjd1312). The fine powder was used immediately for the extraction of the essential oil.

The extraction of the oil was done using the standard of Official Methods of Analysis of the Association of Official Analytical Chemists International, AOAC (2006). About 50 g of fine powder of *piper guineense* fruits was properly wrapped in a filter paper and put in an extraction thumble where it was washed, dried using a drying oven, and allowed to cool down in dessicators prior weighing. It was then placed in a soxhlet Extraction chamber and the oil was extracted using 500ml of 99% n-Hexane in a flask, within 4 hours. After extraction, the solvent was recovered with rotary evaporator and crude extract recollected. The flask and its contents were allowed to cool down in a desiccators and further weighed. The percentage of the oil gotten was 4.2%.

A sample of the essential oil was used to test for the presence of terpenes before commencement of beta caryophyllene extraction, using the method of Godswill *et al* (2014),where 0.5ml of acetic anhydride was mixed with 1ml of sample extract and a few drops of conc. H2SO4. A blush green precipate indicated the presence of terpenes

Separation of Beta-Caryophyllene, BCP) Fraction from *Piper guineense* Fruits

This was done according to the method of Dante, A (2022). The oil content was measured into a flask and 2.5% NaOH was added to it at a volume ratio (oil to NaOH) of 1:5. The mixture was allowed to settle and thereafter stirred using a magnetic stirrer for about 3 hours. After wards, it was left in the separating funnel until two layers were formed. The top layer in the funnel contained beta-caryophyllene. The content in the top layer was isolated and further subjected to fractional distillation under reduced pressure. Afterwards, the content was subjected to re-distillation to isolate beta-caryophyllene at temperatures above 1700 C. The isolated beta-caryophyllene was analyzed using Gas-Chromatographic-Mass Spectrum (GC-MS) analysis for confirmation of beta cafyophyllene. Beta-caryophyllene fraction yield after fractional distillation was 1.02g.

Purchase and concentration of Oxaliplatin and Standard drug; Duloxetine

Oxaliplatin was purchased in powder form from a pharmaceutical store in Enugu. For storage purposes for 30 days, the method of Mehta *et al* (2015) was adopted where a stock solution of 1mg/ml in 5% dextrose solution was prepared for administration by injection as against unstable saline solutions (Mehta *et al*., 2015). A dose of 4mg/kg of body weight of rat was administered as oxaliplatin dose therapy. Mg/kg of body weight of rat was written throughout was mg/kg.

Duloxetine was purchased from a pharmaceutical store in Enugu. It was prepared according to the method of Meng *et al* (2019). Duloxetine HCL was mixed in 0.9% sterile saline and used at a dose of 10 mg/kg (1 hour prior to treatment with Oxaliplatin) as the standard drug of this experiment. Precautions were taken to minimize animal suffering.

Duloxetine is effective in combating the effects of CIPN by oxaliplatin, Paclitaxel, Vincristine or Bortezomib in patients (da Silva Oliveira, *et al*., 2018). . Over the years, the drug has shown the most promise for the treatment of CIPN compared to other drugs (Taejoon, *et al*., 2020; Zhang, *et al.*, 2017). Duloxetine is recommended by American Society of Clinical Oncology and European Society for clinical situation such as in Medical Oncology. It is one of the drugs used to combat peripheral neuropathy (Fidyt, *et al*., 2016; Sharma, *et al.*, 2016).

Therapeutic Administrations of Oxaliplatin and Beta-caryophyllene

The modified method of Jonathan, *et al* (2021) was adopted due to its close resemblance to clinical dosage regimen of Oxaliplatin (OXA) and acute neuropathy. From the first day of treatments onwards , the treatments with OXA (4 mg/kg) was injected intraperitoneally every 48 hours for 20 days, totaling 11 doses of OXA (days 0, 2, 4, 6, 8, 10, 12, 14,16,18,20). Administration was done in the morning. Beta-caryophyllene treatment was given daily by oral gavage for low and high dose (25mg/kg and 50 mg/kg respectively) starting from day 1 for 21 days. Administration was done in the late hours of the afternoon.

Experimental Design of the study

The experimental animals were divided into five (5) group of Eight (8) male wistar group. Groups were treated with normal saline, Oxaliplatin, Duloxetinee and beta-caryophyllene accordingly as tabulated below:

Table 1: Groups and the dose of agents used for treatment/administration

Group	Treatment/Drug Administered	Doses of Agents administered to the group
Group 1	Normal Saline	10 ml/kg b.w
Group 2	Oxaliplatin (OXA)	4 mg/kg b.w
Group 3	OXA + Duloxetine	4 mg/kg b.w + 10 mg/kg b.w
Group 4	OXA +beta-caryophyllene (BCP)	4 mg/kg b.w + 25 mg/kg b.w
Group 5	OXA + BCP	4 mg/kg b.w + 50 mg/kg b.w

Number of animals per group, n= 8. mg/kg b.w = milligram per kilogram of body weight of animal. OXA was given at days 0, 2, 4, 6, 8, 10, 12, 14, 16, 18 and 20. Normal saline, Duloxetine and BCP were given daily for 21 days respectively.

After 21 days of administrations, blood sample was collected by cardiac puncture after euthanasia using 5ml syringe. Haematological analysis of the blood samples was performed in an automated haematology analyzer (BC-2300 model, Mindray Medical Co., China) with the procedure carried as specified by the producer. The parameters which were evaluated included: red blood cells count(RBC), haemoglobin (Hb), packed cell volume (PCV), mean corpuscular volume (MCV); mean corpuscular haemoglobin (MCH); mean corpuscular haemoglobin concentration (MCHC); platelets (PLT); total leukocytes count (TLC) count and differential leukocytes count (WBC) counts were obtained at once for each blood sample.

Statistical Analysis and Data Analysis

Every parameter was analyzed statistically using One-Way Analysis of Variance (ANOVA) and the student Newman-Keul Post-hoc test using IBM SPSS version 20. The data were displayed as mean ± standard error of mean (SEM) in a tabular form. For the mean of the values, a value of< 0.05 was considered statistically significant.

Ethical Clearance

Ethical clearance was obtained from the Faculty of Basic Medical Sciences, College of Medicine and Health

Sciences, University of Nigeria, Enugu Campus. Study Ethical Clearance no: ABSU/REC/MBR/050

RESULTS AND DISCUSSION

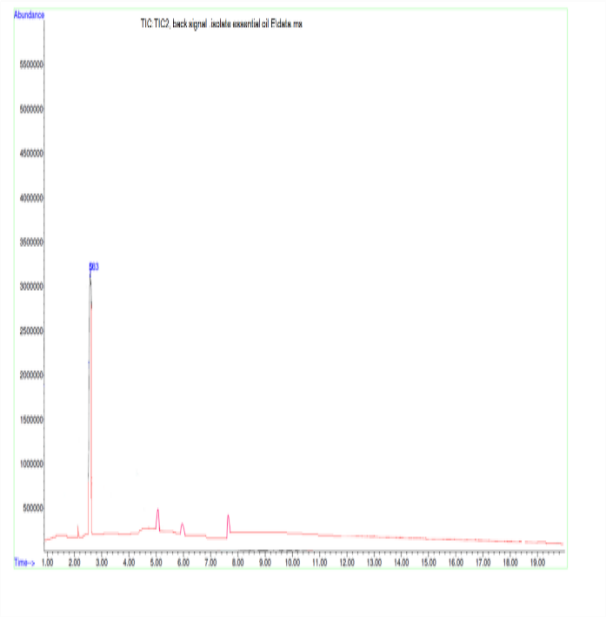

Figure 1: GCMS of Beta-caryophyllene Fraction isolated from N-hexane Fraction of *Piper guineense.*

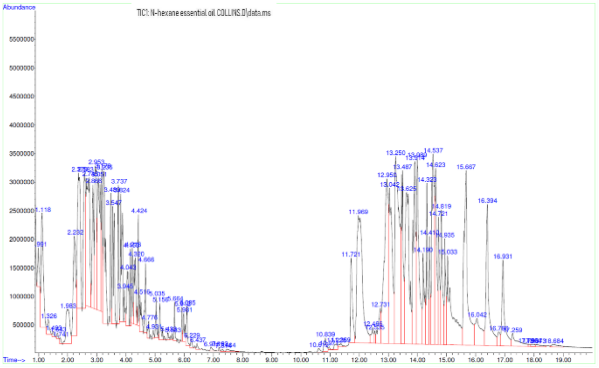

Figure 2 : Chromatography of N-Hexane Fraction of Essential oil of *Piper guineense*

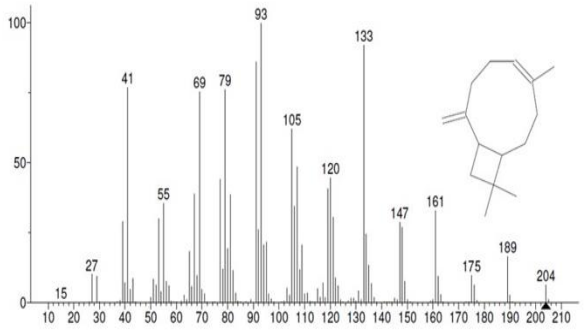

Figure 3: Mass spectrum of beta-caryophyllene (compared with database of National Institute of Science and Technology (NIST) 2014)

Lethal dose evaluation of Beta Caryophyllene

Table 2: Stage 1 Acute toxicity (LD_{50}) evaluation of Beta Caryophyllene in rats

Group	Dose (mg/kg)	No. of Deaths	Percentage of mortality	Observations
1	25	0/3	0.00	No mortality observed, instead animals remained active and physically stable.
2	100	0/3	0.00	No mortality observed, instead animals remained active and physically stable
3	500	0/3	0.00	No mortality observed, instead animals remained active and physically stable

Table 3: Stage 2: Acute toxicity (LD_{50}) evaluation of Beta Caryophyllenein rats

Group	Dose (mg/kg)	No. of Deaths	Percentage of mortality	Observations
1	560	0/3	0.00	No mortality observed, instead animals remained active and physically stable.
2	1000	0/3	0.00	No mortality observed, instead animals remained active and physically stable.
3	2000	0/3	0.00	No mortality observed. Animals were initially calm but regained physical activity within one hour of administration.

The data as shown in Tables 2 and 3 indicated that in all dose groups, none of the animals died, with each group showing a mortality rate of 0.00%. This consistent result across different doses suggests that the substance tested does not have immediate lethal effects within the tested range. Additionally, it was observed that the animals in all dose groups remained active and physically stable. It showed consistencies with safety data sheets of beta-caryophyllene (Agilent, 2019) supporting the conclusion that the substance does not cause acute toxicity or adverse physical reactions in the tested doses. The lethal dose evaluation confirmed that beta-caryophyllene oral consumption is safe for up to 2000mg/kg as reported by da Silva Oliveira *et al* (2018).However, safety data sheet (2019) of Hazard Communication Standard of Occupational Safety And Heath Administration (OSHA's HCS) indicated that it has an oral toxicity of 4,716 mg/kg.

Hematological Effect of fractionated beta-caryophyllene and Duloxetine in Oxaliplatin therpay

Table 4: Effect of Beta Caryophyllene administration on haematological parameters in oxaliplatin-induced peripheral neuropathic rats.

Treatment	Normal control	Oxaliplantin (4 mg/kg) only	Duloxetine (10 mg/kg) + Oxaliplantin (4 mg/kg)	B-Caryophyllene (20 mg/kg) + Oxaliplantin (4 mg/kg)	B-Caryophyllene (50 mg/kg) + Oxaliplantin (4 mg/kg)
RBC ($x10^6/mm^3$)	7.00 ± 0.05^{e}	5.13 ± 0.09^{a}	5.60 ± 0.12^{b}	6.21 ± 0.06^{c}	6.63 ± 0.03^{d}
PCV (%)	45.33 ± 0.33^{d}	34.00 ± 1.15^{a}	37.00 ± 0.58^{b}	41.00 ± 0.58^{c}	42.67 ± 0.33^{c}
Hb (g/dl)	15.83 ± 0.09^{e}	11.23 ± 0.15^{a}	12.27 ± 0.15^{b}	14.10 ± 0.10^{c}	14.50 ± 0.12^{c}
WBC ($x10^3/mm^3$)	8.91 ± 0.09^{c}	7.88 ± 0.10^{a}	8.31 ± 0.22^{ab}	8.23 ± 0.04^{ab}	8.44 ± 0.16^{b}
PLT ($x10^3/mm^3$)	287.67 ± 9.17^{a}	284.33 ± 4.06^{a}	297.00 ± 15.31^{a}	303.67 ± 8.67^{a}	301.33 ± 8.69^{a}
MCV (fl)	64.79 ± 0.17^{a}	66.28 ± 1.10^{a}	66.09 ± 0.43^{a}	65.98 ± 0.36^{a}	64.35 ± 0.27^{a}
MCH (pg)	22.63 ± 0.04^{b}	21.92 ± 0.10^{a}	21.91 ± 0.20^{a}	22.69 ± 0.07^{b}	21.87 ± 0.09^{a}
MCHC (g/dl)	34.93 ± 0.10^{b}	33.09 ± 0.71^{a}	33.16 ± 0.13^{a}	34.40 ± 0.30^{b}	33.98 ± 0.14^{ab}

The data is displayed as mean ± standard deviation (n = 8). In comparison to paired values across the rows, the means with separate letter superscripts differ significantly at $P < 0.05$. RBC= Red blood cells, PCV= packed cell volume, Hb= hemoglobin concentration, MCV= mean Corpuscular Volume, MCH= Mean Corpuscular Hemoglobin, MCHC= Mean Corpuscular hemoglobin Concentration.

As shown in table 4, beta-carophyllene, BCP increased the serum red blood cell count in a dose dependent manner (6.21±0.06 and 6.63±0.03) when compared to oxaliplatin monotherapy (5.13±0.09) and the standard drug for pain, Duloxetinee (5.60±0.12), at $P < 0.05$. However the low and high doses of BCP caused non-dose dependent increases in hematocrit and hemoglobin levels (Hb= 14.10±0.10, 14.50±0.12 and PCV=41.00±0.58, 42.67±0.33) and leucocytes levels (8.23±0.04, 8.44±0.16) when compared to oxaliplatin and duloxetine therapy (PCV= 34.00±1.15, 37.00±0.58; Hb=11.23±0.15, 12.27±0.15 and WBC = 7.88±0.10, 8.31±0.22). This could be an indication of the anemia and neutropenia witnessed in oxaliplatin therapy as seen in other works (Ain, *et al*., 2017). This means that patients on oxalilatin therapy may be susceptible to infections while preentig signs that are common in anemic conditions such as tachycardia, fyspnea, pallor, fatique

and weakness. This study also showed that BCP may protection over the oxidative effects of oxaliplatin therapy. The result is consistent with hematological findings of BCP in other model of Athritis (Saleem, *et al*., 2025). The effects of BCP is believed to be through the activation of the CB2 receptors of the endocannobinoid system pathway leadimg to its anti-inflamatory and antioxidant effect as against the systemic inflammation and oxidative stress associated with oxaliplatin therapy.

Even though oxaliplatin reduced platelets count, this reduction was not significant (284.33±4.06) when compared to BCP treatments (303.67±8.67 and 301.33±8.69) at $P < 0.05$. This work doesn't agree with Ain, *et al* (2017) who noticed a significant decrease in platelets with 0.8mg/kg and Ito, *et al* (2018). This decrease may be partly due to two issues. The first issue is the fact that the work of Ain, *et al* (2017) was a preventive study rather than curative. The second issues is that the duration of administration of oxaliplatin is too short (7 days) as studies have shown that the thrombocytopenia experienced in oxaliplatin therapy usually start at day 5 and become more prominent at day 10 after which platelets levels begins to rise and peak almost at day 21 (Andre, *et al*., 2004). This recovery was also noted by Woo *et al* (2015) who observed it after the patient experiences thrombocytopenia and neutropenia at the early days of oxaliplatin therapy. Also this work doesn't agree with Ito *et al* (2018) who noticed significant decreases in oxaliplatin therapy when given once a week at higher doses of 5 and 8 mg/kg. Cassidy and Misset (2002) and Devanabanda and Kasi, (2023) observed a continuous decrease in Platelet count in Oxaliplatin co-therapy, suggesting that the persistent thrombocytopenia may not be a function of oxaliplatin but of the other drugs co-administered (fluorouracil)

The study also showed that there was no significant difference between oxaliplatin, duloxetine and BCP therapy on MCV, MCH and MCH. However they reduced the levels of MCH and MCHC when compared to the normal group. This is very evident in oxaliplatin therapy as studies have similar results in conditions associated with suppressed bone marrow activity but chronic anemia as commonly seen in both cancer and chemotherapy (Xu, *et al*., 2016). This suggest that patients on oxalipatin are more likely to suffer normocytic chronic anemia rather than aplastic or hemolytic anemia, suggesting that stoppage of oxaliplatin should normalize the red blood cells' capacity.

CONCLUSION

This study has demonstrated that oxaliplatin could induce anemia and leucopenia along its already established dose-dependent neuropathic effect. However, the study has shown that BCP could be more effective than duloxetine in ameliorating the anemic and leucopenic effect of oxaliplatin. In addition, oxaliplatin seems to have no adverse effect on platelet count suggesting that the thrombocytopenia observed in clinical studies involving co-administration of oxaliplatin may not be from the oxaliplatin but from the drug it was co-administered with. Further research and investigation should be carried out to clarify the actual impact of these drugs.

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