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The Inhibitory Effect of Cisplatin (CDDP) and Paclitaxel (PAX) on the activity of CYP_{450} 2E1 and 3A1/2 in Hepatic microsome Isolated from normal and *Portulica Oleraceae* seeds Pretreated Rats

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Abstract Previous studies have shown that *Portulica Oleraceae* ethanolic extract can significantly modulate the activity of several drug metabolizing enzymes, this may affect the bioavailability of drugs resulting in over dose or less therapeutic effects. This study was designed to assess the inhibitory effects of cisplatin (CDDP) and paclitaxel (PAX) on two types of CYP_{450} isoformers namely: CYP2E1 and CYP3A1/2 in hepatic microsomes isolated from normal and *Portulica Oleraceae* pretreated rats. CDDP and PAX were used by different concentrations to hepatic microsomes isolated from normal and *Portulica Oleraceae* (250 mg/kg/day) pretreated rats for 10 days after receiving pyrazole or dexamethasone for induction of CYP2E1 and CYP3A1/2 respectively. Addition of CDDP or PAX by (10, 50 and 100 μM) to hepatic microsomes from normal or *Portulica Oleraceae* pretreated rats caused a concentration dependent inhibition of CYP2E1, with an evidence of less inhibition in *Portulica Oleraceae* pretreated microsomes particularly at higher concentration. Cisplatin (CDDP) (10, 50 and 100 μM) caused a concentration dependant inhibition of CYP3A1/2 that was enhanced by *Portulica Oleraceae* pretreatment. The inhibitory influence of PAX (10, 50 and 100 μM) on CYP3A1/2 decreased with increasing the drug concentration and this inhibition was augmented by *Portulica Oleraceae* pretreatment. PAX has an inhibitory effect on 2E1 and 3A1/2 isozymesmore than CDDP. Pretreatment with *Portulica Oleraceae* decreased an inhibition in 2E1, while the inhibition was enhanced by 3A1/2. *In conclusion*, *Portulica Oleraceae* pretreatment attenuated the inhibitory influence of cisplatin (CDDP) and paclitaxel (PAX) on CYP2E1 activity and magnified their inhibition on CYP3A1/2. Thus, use of *Portulica Oleraceae* ethanolic extract with drugs should raise concern for drugs–herb interactions.

Keywords *Portulica Oleraceae*, Cisplatin, Paclitaxel, CYP 2E1, CYP 3A1/2 isoenzymes

Introduction

Herbal extracts have many properties like antioxidant, anti-allergic, anti-inflammatory, antiviral, anti-proliferative and anti-carcinogenicity [1-2]. Natural antioxidants, which are capable of protecting the cells from oxidative injury, should be included in the potential antioxidant therapy. Therefore, there is a need for identifying alternative, natural and safer sources of antioxidants [3].

Portulaca oleracea (PO) (family of Portulacaceae) is a genus of succulent herbs distributed in the warmer parts of the world and it is a well-known edible plant. Many active compounds are present including: Alkaloids (major components), flavonoids, monoterpenoids, coumarins, and volatile oils [4-5]. In *PO*, the flavonoids levels vary according to the part of the plant; the highest levels are present in seeds, root followed stem and leaf; and seven different flavonoids are present in this plant, including kaempferol, myricetin, luteolin, apigenin, and quercetin [6]. *PO* is a commonly found species and a medicinal food for human consumption, it contains minerals, proteins,

carbohydrates, β-carotene, vitamins and fatty acids [6-7]. This plant is also used as folk medicine in many countries with various pharmacological effects such as: hepatoprotective [9-10], anti-inflammatory [5], and strong anti-oxidant [11]. Among the bioactive components and biological activities assigned to the *PO*, the presence of catecholamines [12] and its antioxidant and anti-inflammatory actions [13] deserve to be highlighted. Moreover, the *PO* extracts decreased apoptosis and oxidative-stress-induced neuro-degeneration caused by the pesticide rotenone [14-15]. Dursun *et al*. [16] and Abd El-Aziz *et al.* [17] revealed that the bioactive compound and health effects of *portulaca oleracea* were alkaloids, Beta-carotene, Beta-sitosterol, caffeic acid, catechol, chlorophyll, coumarin, DHA, EPA, ferulic acid, flavonoids, saponin and tannin acts as analgesic, antiaggregant, antiarhritic, antiartheriosclerotic, anticancer (breast, colon, fore stomach, liver, skin) activities.

Our previous studies of Nermien [18] stated that, *Portulica oleraceae* (PO) (Purslane) seeds and leaves reduce reactive oxygen species (ROS) and the toxic effect of CCl_4 at high dose which exert a highly percentage of inhibition. These data suggest that purslane herb extract have a beneficial effect on reducing the toxicological effects as anti-inflammatory and the protective individual for oxidative stress diseases. Also, our previous studies by Nermien [19] stated that, *Portulica Oleraceae* (seeds) exhibits good antioxidant, anti-inflammatory and variable cytotoxic activities on human breast (MCF-7) cancer cell line which may provide support for this extract potentiality as a chemo preventive agent and as a promising candidate for antineoplastic drug development.

J**ú**lia *et al.* [20] stated that, the toxic effects of CDDP are associated with the production of reactive oxygen species (ROS) within the mitochondria. CDDP exposure results in an intracellular ROS increase in normal cells [21-22], and treatment with antioxidants can ameliorate cisplatin toxic effects on several organs [23-25], suggesting an involvement of oxidative stress in the pathogenesis of cisplatin-induced dose-limiting toxicities. However, the molecular mechanisms by which ROS are formed still remain unclear [26].

Cisplatin (platinum based drug) [27-28] and Paclitaxel (originally derived from the bark of the Pacific yew tree Taxus brevifolia) [29-30] are potent antineoplastic agents used for the treatment of a wide range of cancers. Being chemotherapeutic drugs, they are often associated with various degrees of interaction with the hepatic metabolizing enzymes. On the other side, paclitaxel is primarily metabolized by CYP3A1/2 and CYP2C8 into virtually inactive component exerted in bile [31]. Predating to that, Kostrubsky *et al.* [32] reported that paclitaxel at high concentrations, higher than 10 μM resulted in inhibition of CYP3A activity in isolated human hepatocytes.

Paclitaxel (PAX) is oxidized to products that are less antineoplastic than the parent drug. The antineoplastic effects of taxanes observed *in-vivo* are apparently related to metabolic rates rather than to metabolic profiles [33].

The CYP monooxygenase super family is the most important phase I metabolic enzyme system in the liver. CYP is responsible for the metabolism of a wide variety of xenobiotics and endogenous compounds. The CYP_{450}-dependent metabolism has also been demonstrated to be responsible for the toxicity of various xenobiotics [34-36]. In human, the major drug-metabolizing CYPs are CYP1A2, CYP2A6, CYP2C9, CYP2C19, CYP2D6, CYP2E1, and CYP3A4 [37]. Inhibition and induction of these CYP isoenzymes may result in toxicity or therapeutic failure and are the most common causes of drug–drug interactions [38-39]. CYP3A4 is present in abundance in human liver microsomes, and it metabolizes 50 % of clinical drugs, endogenous compounds and environmental pollutants [40]. For this reason, it is considered an important isozyme for the investigation of drug interactions via CYP. These reactive and toxic intermediates formed during its action increase the formation of oxygen and hydroxyl free radicals that damage cellular structure and cause hepatotoxicity [41-42].

Cytochrome P_{450} is a hemoprotein super family of isoenzymes that are responsible for the metabolism of a wide variety of foreign chemicals including anticancer drugs [34, 43]. P450s system is mainly localized in the liver more abundant than in any other organs such as lung, kidney or intestine [36]. Of various P_{450} isoenzymes, CYP2E1 is mainly expressed in liver and in small amounts in kidney, lung and gut [44-45]. It is a major isoenzyme involved in the bioactivation of chemicals and drugs to toxic metabolites supporting its role in hepatotoxicity by many drugs [45]. CYP2E1 itself is also an effective enzyme for ROS production, exhibiting enhanced NADPH oxidase activity, and elevated rates of O^{2-} and H_2O_2 production even in the absence of substrate [46-47].

To our knowledge, there are no reports regarding the modulatory effect of *Portulica Oleraceae* (PO) pretreatment on the inhibitory influence of cisplatin (CDDP) and paclitaxel (PAX) on certain P_{450} enzymes in isolated rat hepatic

microsomes from rat liver. Thus, the aim of this study was directed to investigate the inhibitory effects of CDDP and PAX on the activity of two CYP isoenzymes involved in drug metabolism namely CYP2E1 and CYP3A1/2 in isolated hepatic microsomes from normal and *Portulica Oleraceae* (PO) pretreated rats, to explore the possible modulatory effect of prior treatment with *Portulica Oleraceae* on the response of these CYP isoenzymes to the inhibitory effect of these anticancer drugs.

Materials and Methods

Drugs and chemicals

Paclitaxel (PAX) was obtained from filaxis laboratories; Cisplatin (CDDP) was obtained from Korea United Pharm (KUP). Pyrazole, dexamethasone, erythromycin, p-nitrophenol and all other chemicals used throughout the present work were obtained in analytical and purified grade and were purchased from Sigma Chemical Co., St. Louis, USA.

Preparation of Portulica Oleraceae ethanolic extract

Seeds of *Portulica Oleraceae* were collected from Applied Research Center for Medicinal Plants (ARCMP), washed, dried, extracted by 80% ethanol according to Lee *et al.* [48], and the extract was lyophilized, and the lyophilized powder (ethanolic extract) was resuspended in saline and used in appropriate dose.

Experimental animals

Male Wistar albino rats weighed 200 ± 240 g were obtained from the animal house of the National Organization for Drug Control & Research (NODCAR), Giza, Egypt. Animals were housed under controlled temperature (25 ± 2 ºC) and constant light/dark cycle (12/12 h). They allowed free access to a standard rodent diet and water. The investigations complies with the guide for care and use of laboratory animals published by US National institutes of Health (NIH NO.85-23, revised in 1985) and was approved by the Ethics Committee for animal experimentation at Faculty of Pharmacy, Cairo University.

Rats were divided into 4 groups of 6 animals each. Group 1 and 3 received at the beginning *Portulica Oleraceae* ethanolic extract at an oral dose of 250 mg/kg/day [49] for 10 consecutive days. Group 1 and 2 received i.p. dose of pyrazole 250 mg/kg/day for two days to induce CYP2E1 [50] which started at the 9th day. Group 3 and 4 received i.p. dose of dexamethasone 100 mg/kg/day for 3 days to induce CYP3A1/2 [51] which started at 8th day.

Preparation of hepatic microsomes

24 hrs after the last treatment, rats from each group were sacrificed by decapitation and liver samples were isolated quickly and rinsed with ice-cold saline, dried. Preparation of hepatic microsomes was performed as described by Lake [52]. Briefly, liver samples were homogenized in 25 mM Tris–HCl (pH 7.5) containing 1 mM EDTA and 0.25 M sucrose. The homogenate was centrifuged at 18,000g for 20 min. The supernatant was then centrifuged twice at 100,000g for 60 min. The resulting microsomal pellets from each experimental group were pooled and resuspended in 0.1 M sodium phosphate buffer (pH 7.5) containing 20% glycerol and stored at −80 ºC until used. Protein concentration in the microsomal fraction was determined as previously described by Lowry *et al.* [53] using bovine serum albumin as a standard.

Measurement of CYP2E1 and CYP3A1/2 activities in presence of different concentrations of cisplatin (CDDP) and paclitaxel (PAX)

CYP2E1 activity was determined by using p-Nitrophenol hydroxylation assay as described by Alexidis *et al*. [34]. Briefly after incubation of hepatic microsomes (1-1.5 mg protein) from either untreated or *Portulica Oleraceae* pretreated animals with 5 mM p-nitrophenol and in the presence of (10, 50, 100 μM) of either cisplatin (CDDP) or paclitaxel (PAX) at 37 ºC for 15 min, 20%trichloroacetic acid was added to terminate the reaction, followed by addition of 10 mmol NaOH to develop the color. The enzyme specific activities were determined by quantifying the production of p-nitrocatechol spectrophotometrically at 510 nm (UV-Unicam spectrophotometer) and expressed as μmol/min/mg protein. CYP3A1/2 activity was measured colorimetrically by the measurement of formaldehyde

liberated due to N-demethylation of erythromycin based on the Hantzsch reaction as described by Alexidis *et al.* [34]. Briefly after incubation of hepatic microsomes (1-1.5 mg protein) from either untreated or *Portulica Oleraceae* pretreated animals with 5 mM erythromycin and in the presence of (10, 50, 100 µM) of either cisplatin or paclitaxel at 37 ºC for 15 min, together with 20 mM semicarbazide and 1 mM NADPH to initiate the reaction. After 15 min, 25% $ZnSO_4$ was added to terminate the reaction followed by the addition of Nash reagent. The color developed by the reaction of Nash with the produced formaldehyde was measured spectrophotometrically (UV-Unicam) at 415 nm. The enzyme specific activity was expressed as µmol/min/mg protein.

Data analysis

The results are presented as mean ± S.E. the values were obtained from the mean of triplicate incubations. The statistical analysis was conducted by using the SPSS program version 11.0 at P-value less than 0.05. An independent t-test, one-way ANOVA and The strength of association between pairs of variables was assessed by LSD comparison.

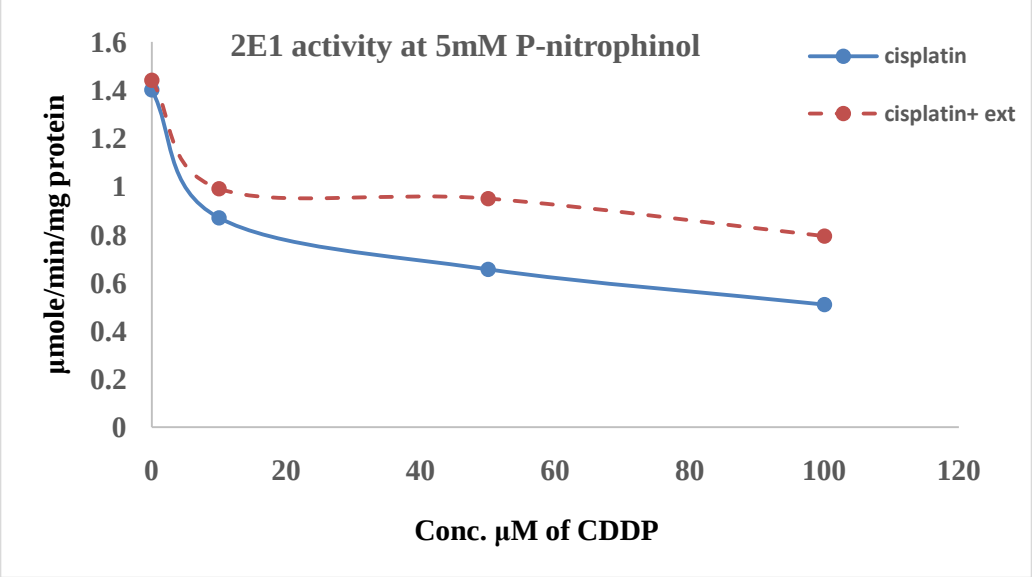
Results

The inhibitory effect of cisplatin (CDDP) and paclitaxel (PAX) on the activity of CYP2E1 in hepatic microsomes isolated from normal and Portulica oleraceae pretreated rats

Figure 1(A and B) demonstrated that at 5 mM p-nitrophenol, addition of cisplatin (CDDP) or paclitaxel (PAX) by the three concentrations (10, 50, 100 µM) resulted in a sustained gradual reduction in hepatic normal microsomal CYP2E1 enzyme activity in concentration dependant manner. However, incubation of CYP2E1 enzyme from the *Portulica oleraceae* pretreated rats microsomes with cisplatin and paclitaxel at the above concentrations resulted in less inhibition of its activity particularly at higher concentrations of the drug.

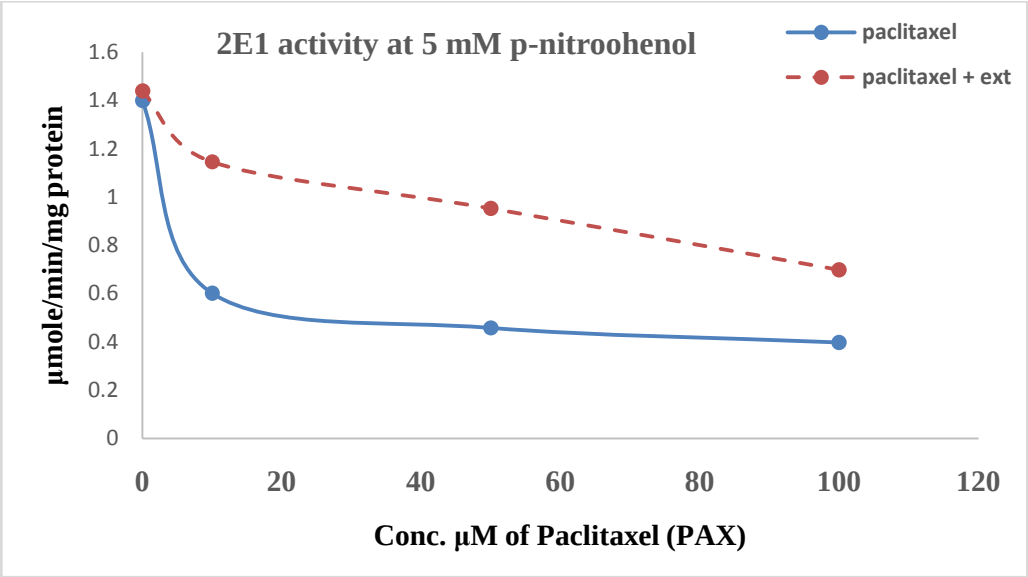
The inhibitory effect of CDDP was increased by increasing concentration but *Portulica oleraceae* pretreated rats resulted in decreased the inhibition by increasing concentrations. CYP2E1, the inhibitory effect of PAX was more than CDDP which lead to decrease the activity of 2E1. The low concentration of PAX by the concentration of 10µM was more effective on the activity of 2E1 than the highest concentration of 100µM.

(A)



Values are expressed as mean ±S .E.M.

(B)



Values are expressed as mean ±S .E.M.

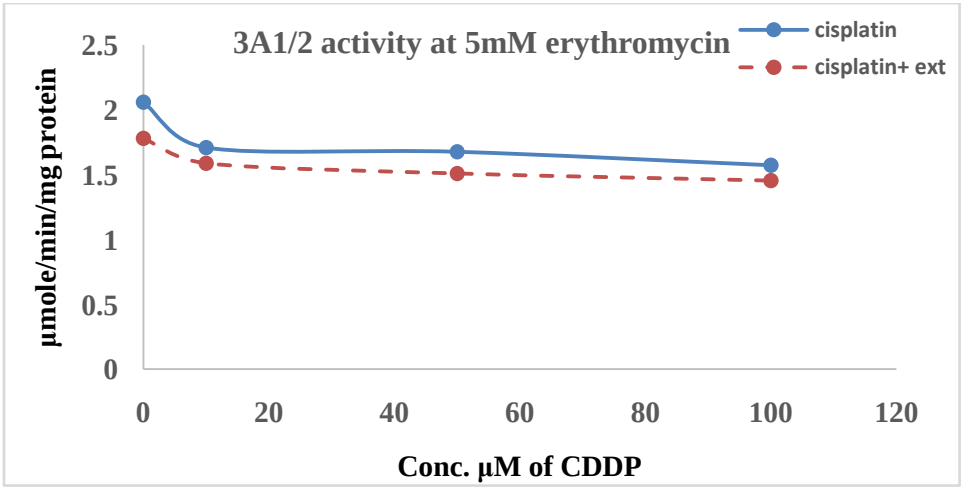
Figure 1: The inhibitory effect of Cisplatin (A) and Paclitaxel (B) on the activity of CYP2E1 in hepatic microsomes isolated from normal (_____) and Portulica oleraceae (----) pretreated rats at concentration 5mM of p-nitrophenol

The inhibitory effect of cisplatin (CDDP) and paclitaxel (PAX) on the activity of CYP3A1/2 in hepatic microsomes isolated from normal and Portulica Oleraceae pretreated rats

Data compiled in Figure 2(A and B) revealed that at substrate concentration of 5 mM erythromycin, incubation of the normal hepatic microsomes with cisplatin (10, 50 and 100 µM) showed gradual decline in CYP3A1/2 enzyme activity. While upon its incubation with paclitaxel, the inhibitory effect of the drug appeared to decrease by increasing the drug concentrations. Upon, addition of cisplatin or paclitaxel by the above three concentrations to hepatic microsomes from *Portulica Oleraceae* pretreated rats, the drugs exhibited more inhibition in the activity of CYP3A1/2 compared to the normal microsomes values particularly at high drug concentration.

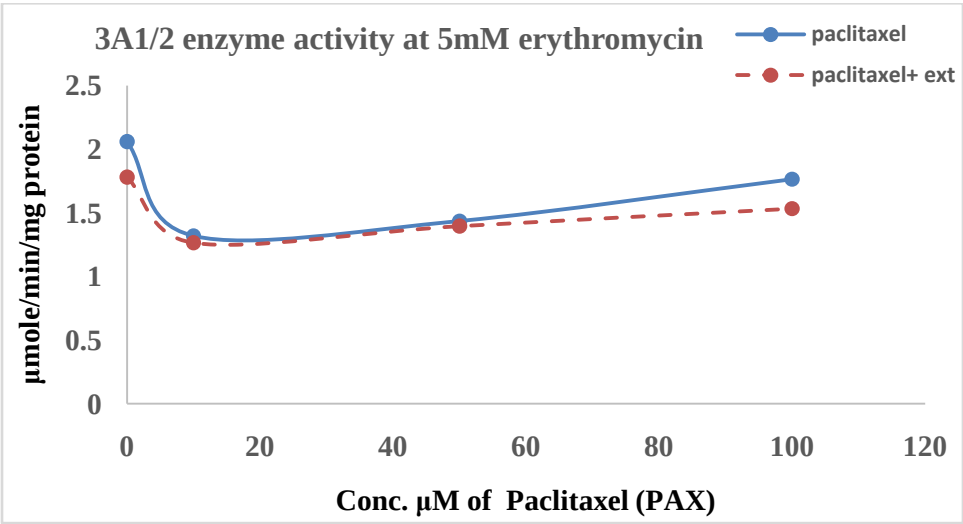
The inhibitory effect of PAX at 10µM was enhanced while this effect was decreased by increasing the concentration which increases the activity of 3A1/2. The inhibitory effect at high concentration of 100µM after *Portulica Oleraceae* pretreated rats was enhanced and the activity of 3A1/2 will decreased.

(A)



Values are expressed as mean ±S .E.M.

(B)



Values are expressed as mean ±S .E.M.

Figure 2: The inhibitory effect of Cisplatin (A) and Paclitaxel (B) on the activity of CYP3A1/2 in hepatic microsomes isolated from normal (_____) and Portulica oleraceae (----) pretreated rats at concentration 5mM of p-nitrophenol.

Discussions

Cytochromes P_{450} are major oxidative enzymes that metabolize xenobiotics including anticancer drugs. Modulation of these enzymes can dramatically affect cytotoxicity and/or therapeutic efficacy of these drugs. In this study, the aim of this study was to investigate the inhibitory potency of cisplatin (CDDP) and paclitaxel (PAX) toward two P_{450} isoforms CYP2E1 and CYP3A1/2 occurring in differentially induced rat liver microsomes isolated from normal or *Portulica oleraceae* pretreated rats. p-Nitrophenol hydroxylation and N-demethylation of erythromycin reactions were chosen for the study of the inhibition of CYP2E1 and CYP3A1 activities respectively.

The results of the present study clearly revealed that the activity of CYP2E1 was significantly inhibited by the three concentrations of CDDP and PAX (10, 50, 100 µM) after incubation of the hepatic microsomal fractions from normal rats with the drugs. The inhibitory effects of both drugs increased with increasing the drug concentrations in a concentration dependent manner. These results also indicated that PAX inhibited p-nitrophenol hydroxylation more strongly than CDDP. The inhibitory effect of CDDP on CYP2E1 was in line with the early observation of Masubuchi *et al.* [54] who observed a transient decrease in CYP2E1 activity after treatment with CDDP. This transient inhibition may be due to a direct effect of CDDP on CYP2E1. Moreover, Vaclavikova *et al.* [55] reported that CYP2E1 might be involved in PAX metabolism and cytotoxicity, since uninduced rat microsomes did not change the effect of the drug, whereas CYP2E1-induced rat microsomes increased its cytotoxicity. Indeed, the inhibition of CYP2E1 by PAX has not yet studied and defined.

Owing to the roles played by CYP2E1 in mediating carcinogenesis and chemical cytotoxicity, modulation of CYP2E1 is an important issue in organ and tissue protection. Several studies have shown that *Portulaca oleracea* display several biological activities, such as anticancer, antioxidation, anti-inflammation, and immunity enhancing properties [6, 56-58]. Therefore, the inhibition of CYP2E1 by *Portulica oleraceae*, may have a crucial role in these pharmacological activities. CYP2E1 is a major isoenzyme involved in the bioactivation of chemicals and drugs into toxic metabolites which may contribute to their tissue toxicity, *Portulaca oleracea*, have a suppressive effect on the growth of HeLa and HepG2 cells *in vitro*, suggesting that the sulfation of *Portulica oleraceae* polysaccharides increases the cytotoxicity in tumor cells [59]. In addition, other bioactive compounds such as cerebrosides, homoisoflavonoids, and alkaloids also show *in-vitro* cytotoxic activities against human cancer cell lines [60]. Pretreatment with *Portulica oleraceae* had been previously reported to have a protective effect against carbon tetrachloride-induced hepatotoxicity [61]. It appeared that the PO reduced the acute liver injury induced by CCl_4

involving the enhancement of NF-*κ*B activity, suggesting that, the edible plant *Portulaca Oleracea L.*, may be used to protect against toxic effects of CCl_4 and other chemical agents in liver. Thus, the hepatoprotective effect of *Portulica oleraceae* (PO) may be related to inhibition or reduction of CYP2E1 isoforms, via reducing the formation of toxic metabolites.

CYP2E1-mediated metabolism generates reactive oxygen species, such as oxygen and hydroxyl radicals, when these exceed the cellular detoxification systems, it results in oxidative stress with its various pathologic consequences [62]. Oxygen radicals play a key role in liver injury because of their interaction with cellular proteins or DNA [62-63]. CYP2E1 over expression generated oxidative stress in a human hepatoma cell line and induced cytotoxicity to the cells [64], and CYP2E1 induction could alter immune system responses, leading to increased susceptibility to viral infection [65].

Yan *et al.* [66] reported that, alkaloid including tetrahydropalmatine are reported to inhibit cytochromes P_{450} (CYPs) activity *in-vitro*. Also, they suggested that total alkaloid extract (TAE)-induced CYPs activity in the rat liver results from the elevated mRNA levels of CYPs. Co-administration of prescriptions containing Yanhusuo (*Corydalis yanhusuo* W.T. Wang; YHS) should consider a potential herb (drug)–drug interaction mediated by the induction of CYP2E1 and CYP3A1 enzymes. Yan *et al.* [66] revealed that, after treatment of rats for 14 days with total alkaloid extract (TAE) from (Corydalis yanhusuo W.T. Wang; YHS), both the enzyme activity and mRNA level of CYP2E1 were significantly increased at all three (TAE) dosages. The liver injury caused by YHS, may thus have resulted from the induction of the drug metabolic enzyme CYP2E1 by long-term administration of YHS. Drug-drug interactions are of concern when low-dosage TAE from YHS as well as substrates of CYP2E1 are administered.

Rosmarinic acid reduced CYP2E1 in rats treated with ethanol which induced CYP2E1 [67]. Turmeric pretreatment attenuated the inhibitory influence of cisplatin (CDDP) and paclitaxel (PAX) on CYP2E1 activity and magnified their inhibition on CYP3A1/2, thus the use of turmeric with drugs or other medications should raise concern for drugs–herb interactions [68]. Simvastatin (SV) exerted an oxidative stress which may be contributed to hepatotoxicity, while naringenin (NRG) attenuated this toxicity, so it may be of therapeutic use as adjuvant drug. Also, the inhibitory effects of these drugs toward CYP2E1 and CYP3A1/2 activities were dose-dependent. However, other experiments will have to be carried out to investigate the interaction between SV and NRG. If this interaction was confirmed in-vivo in human, these results should be taken into account to adjust doses in order to avoid adverse effects when grapefruit juice or one of its components such as NRG is co administered with SV [42].

At the present study, the activity of CYP3A1/2 was significantly inhibited by (10, 50 and 100 μM) of CDDP after incubation of the microsomal fraction with the drug. The inhibitory effect of CDDP was increased with increasing the drug concentrations (dose-dependent). These findings are in line with Ando *et al.* [69] who reported that CYP3A1/2 activity was moderately inhibited by CDDP at 10 μM concentration. On the other hand, addition of CDDP by the above three concentrations to CYP3A1/2 in microsomes isolated from *Portulica oleraceae* (PO) pretreated rat caused further inhibition of the enzyme activity as compared to the normal control values. Moreover, incubation of normal microsomes with (10, 50 and 100 μM) of PAX in the current study caused a significant inhibition in the activity of CYP3A1/2. However, the inhibitory effects of PAX decreased with increasing the drug concentrations. These results are complying with the work of Kostrubsky *et al.* [32] who demonstrated that treatment of CYP3A1/2 with concentrations of PAX higher than 10 μM caused a dose-dependent decrease in its activity and the amount of its enzyme protein. The same pattern of inhibition was also observed upon the addition of PAX in above concentrations to CYP3A1/2 of microsomes from *Portulica oleraceae* (PO) pretreated rats. The observed inhibition of the activity of CYP3A1/2 in response to *Portulica oleraceae* (PO) pretreatment in this study was in agreement with that of Syed and Paramjyothi [70] and Kimura *et al.* [71] they reported that *Portulica oleraceae* (PO) showed inhibition patterns for CYP3A4 and that human CYP3A4 and rat CYP3A1.

The CYP3A subfamily is the most important hepatic metabolic enzyme in the metabolism of 40% to 60% of all drugs [72]. CYP3A4 is the most abundant CYP in the human liver, where it accounts for 30% of CYPs [73], and rat CYP3A1 is a homolog of human CYP3A4 [74]. CYP3A1 can catalyse the 6β-hydroxylation of testosterone [75] and the metabolism of a large variety of clinical medications, including many pediatric drugs [76], cyclosporin A [77]. CYP3A1 was significantly induced in the rat liver, lung, and intestine at 30 mg/kg (equivalent to the clinical

dosage), suggesting that TAE has the potential to produce CYP3A-mediated drug–drug interactions. Consumption of YHS or YHS-containing products with the substrates of CYP3A should be taken more attention because of the possibility of drug-drug interactions. Yan *et al.* [66] stated that, TAE from YHS significantly induced the mRNA expression and enzyme activity of CYP2E1 and CYP3A1 in the rat liver, lung, and intestine. Furthermore, enzyme activity correlated well with mRNA expression. The results of the present dose–response study in rats suggest that potential CYP2E1 and CYP3A drug-drug interactions are unlikely at clinical dosages of TAE, but need to be considered when high dosages of TAE or TAE-containing products are co administered with substrates of CYP1A2 or CYP2C11. Complex herb (drug)-drug interactions may ensue from the co-administration of YHS with other drugs, which is mediated by CYP2E1 and CYP3A1 enzymes which was inagreement with our results.

Zhou *et al.* [5] revealed that, in addition to flavonoids, another important chemical found in PO which is alkaloids including dopa, dopamine, and noradrenalin and this was in agreement with our results.

Conclusions

This *in-vitro* study showed that *Portulica oleraceae* (PO) ethanolic extract pretreatment modulates the activity of CYP_{450} enzymes, as it had strong inhibitory influence on CYP3A1/2 with a limited effect on CYP2E1. Pretreatment with *Portulica oleraceae* attenuated the inhibitory effects of cisplatin (CDDP) and paclitaxel (PAX) on CYP2E1. However, this pretreatment enhanced the inhibitory influence of these drugs on CYP3A1/2.

Conflict of Interest

The author declares that there are no conflicts of interest.

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