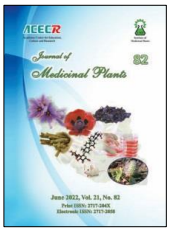
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Research Article

Proapoptotic effect of nanoliposomes loaded with hydroalcoholic extract of *Hypericum perforatum* L. in combination with curcumin on SW48 and SW1116 colorectal cancer cell lines

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ABSTRACT

Background: Colorectal cancer (CRC) continues to be a leading cause of cancer related death in the world and approximately 70 to 75 % of patients with metastatic colorectal cancer survive for up to 1 year after diagnosis. Curcumin (CUR) is a potential chemotherapeutic agent used to treat cancer. There is ample evidence of the inhibitory effects of *Hypericum perforatum* L. extract (HPE) on cell proliferation and its effects on the induction of apoptosis in various human cancer cell lines. **Objective:** The purpose of this study was to investigate the proapoptotic effect of HPE and its nanoliposomes (HPE-Lip) and to scrutinize the synergistic and therapeutic potential of HPE/CUR-loaded nanoliposome (HPE/CUR-Lip). **Methods:** In the present *in vitro* study, SW1116 and SW48 cell lines were cultured and then treated with different doses of HPE, CUR, bare liposome solely (Lip-Sol), and nanoliposomes loaded with HPE (HPE-Lip), CUR (CUR-Lip) and CUR/HPE (HPE/CUR-Lip) for 24, 48 and 72 hours. Cytotoxicity was measured by MTT assay and apoptosis rate by an annexin-V FITC/propidium iodide double-staining method using flow cytometry. **Results:** The results showed that cell viability was inhibited in a dose-dependent and time-dependent manner in all groups compared to the control group. The use of nanoliposomes improved the outcomes. HPE/CUR-Lip exhibited higher *in vitro* cytotoxic and proapoptotic activity against SW1116 and SW48 cell lines ($P < 0.05$). **Conclusion:** The findings of this study suggest that the HPE/CUR-Lip complex could provide a potential strategy to achieve a synergistic effect of HPE and CUR in the treatment of colorectal cancer.

Abbreviations: ANOVA, One-way Aanalysis of Variance; AP-1, Activator Protein 1; Bcl-2, B-Cell Lymphoma 2; JNK, c-Jun N-Terminal Kinase; CRC, Colorectal Cancer; Cox-2, Cyclooxygenase-2; CUR, Curcumin; DMSO, Dimethyl Sulfoxide; DSPC, Distearoylphosphatidylcholine; FBS, Fetal Bovine Serum; FITC, Fluorescein Isothiocyanate; IC_{50}, Median Inhibitory Concentration; HSD, Honestly Significant Difference; HPE, *Hypericum perforatum* extract; Lip, Nanoliposomes; MTT, 3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyl-2H-tetrazolium bromide; NF-κB, nuclear factor κB; PBS, Phosphate Buffered Saline; PS, Phosphatidylserine; PI3K, Phosphoinositide-3 Kinase/protein kinase-B; PI, propidium iodide; PLA, polylactic acid; PPAR-γ, Peroxisome proliferator- activated receptor gamma; ROS, Reactive oxygen species; SOD, Superoxide dismutase

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1. Introduction

Colorectal cancer (CRC) is a condition originating from the epithelial cells lining the rectum or colon, whose incidence is affected by various environmental and genetic factors [1]. It is the third most common cancer worldwide and the second leading cause of cancer deaths, accounting for 880,792 cancer deaths in 2018 [2]. The disease is expected to be diagnosed as common in both men and women by 2020 [3], indicating the importance of the disease prevention and control program [4]. Chemotherapy is one of the cancer treatment strategies, although it is associated with low therapeutic efficacy and high systemic toxicity. In addition, naturally occurring plant products can be administered as both extracts and their derivatives in soothing care. The use of medicinal plants has currently attracted further attention due to the patients lack of serious side effects [5]. Recently, co-delivery of chemotherapy drugs and natural products has been widely considered as a solution to overcome some challenges, including side effects, drug resistance, solubility and pharmacokinetics of various drugs, and drug/dosage ratio control in target tumor cells [6-8]. Many drug delivery systems have been tested to circumvent the bottleneck of providing effective combination chemotherapy, including nanoliposomes that have long been used as an efficient delivery system due to their excellent biocompatibility, optimal degradability, low toxicity, inactivation of the immune system and the ability to use both hydrophilic and hydrophobic drugs [9]. In addition, liposomes can control drug release in combination with an optimized synergistic molar ratio [10]. Thus, co-delivery of drugs could potentially improve anticancer activity based on the synergistic effect of drugs, and offer a new therapeutic approach to CRC treatment.

Hypericum perforatum L. (HP) is a perennial herbaceous plant belonging to the family *Hypericaceae*, which contains multiple groups of effective compounds including naphthodianthrones (e.g. hypericin and isohypericin), flavonoids (e.g. kaempferol, quercetin, quercitrin, rutin, amentoflavone and biapigenin), acylated phloroglucinol derivatives (e.g. hyperforin and adhyperforin), flavan-3-ols, tannins, aromatic acids (e.g. caffeine, *p*-coumaric and chlorogenic [11, 12]. The HP has been prescribing in traditional medicine due to its anti-inflammatory effects. As well, antioxidant, anti-cancer, anti-proliferative, cytotoxic and apoptotic induction activities have also been well studied for this plant [13, 14]. The cytotoxicity of HPE against different cancer cell lines is achieved by activating the apoptotic signal pathways, including caspase activation and cell cycle arrest, and also inhibiting tumor-induced angiogenesis [15, 16]. A recent case-control study of three patients with gastrointestinal cancer documented that long-term use of HP creates a blood-tumor barrier, which may be a sign of its antitumor effects [17].

Curcumin (CUR) is a yellow phenolic compound, which is extracted from the turmeric (*Curcuma longa* L.) rhizomes. Many studies indicated that the CUR has anti-cancer properties such as pro-apoptotic effects, proliferative suppression, induction of apoptosis, inhibition of metastasis and angiogenesis by affecting cell signaling pathways. Evidence suggests that the CUR causes a lower incidence of gastrointestinal cancers such as CRC [18-20].

The present study aimed to produce the liposomes co-loaded with HPE and CUR. Cytotoxic and proapoptotic effects and efficacy of this formulation (dual drug-loaded liposome) were studied and compared with the effect of extract alone and mono drug-loaded liposome in

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the CRC cell lines of SW48 and SW1116 (SW48 cell line has higher invasive properties when compared with the SW1116 cell line).

2. Materials and Methods

2.1. Preparation of plant extracts

In April 2019, fresh HP aerial parts were collected from the suburbs of Yasuj, Kohgiluyeh and Boyer-Ahmad Province (Iran). The voucher specimen of the authenticated plant (voucher no. 0478) was deposited at the herbarium of Medicinal Plants Research Center, Yasuj University of Medical Sciences. To prepare the extract, 300 g of dry powder of HP plant was dissolved in 1200 ml of a mixture of ethanol and distilled water at a ratio of 70:30 and incubated at an ambient temperature for 72 hours. Then, the mixture was filtered through Whatman paper and centrifuged at 3500 rpm for 20 minutes. The supernatant was dried in an incubator. Finally, the resulting semi-solid mass was freshly used.

2.2. Preparation of nanoliposomes

The liposomes were prepared using thin-film hydration method. Briefly, the required amounts of DSPC and cholesterol were dissolved in 1 ml of chloroform and then vacuum evaporation was carried out using a round-bottom flask to obtain a thin lipid film. The lipid film was hydrated in 50 mM of Tris buffer (pH=7.4) at 65 °C for approximately 2 hours. The freeze-thaw cycle was performed by freezing the mixture in liquid nitrogen at -196 °C for 5 minutes and then melting in a water bath at 65 °C and shaking for 5 minutes.

2.3. Cell cultivation

The SW1116 and SW48 cell lines of colorectal cancer were purchased from Pasteur Institute of Iran. This cell lines were cultured in RPMI medium in the presence of 10 % fetal bovine serum (FBS), 100 U/ml of penicillin, and 100 µg/ml of streptomycin, and incubated at 37 ºC, 5% CO_2 and 95% relative humidity. In standard culture methods, the cells were cultured by trypsinization in culture flasks every 48-72 hours to cultivate the log phase cells.

2.4. Assessment of cell viability by MTT assay

The MTT assay was performed to measure the proliferation and viability effects of curcumin solely (CUR-Sol), curcumin-loaded liposome (CUR-Lip), HPE solely (HPE-Sol), HPE-loaded liposome (HPE-Lip), and HPE/CUR-loaded liposome (HPE/CUR-Lip). In summary, the cells were incubated in a 96-well plate with a density of 10^4 cells per well and 100 µl of medium for 24 hours in a CO_2 incubator, followed by the addition of different formulations at different concentrations. Incubations were then performed for 24, 48 and 72 hours. After removal of the PBS, 10 µl of MTT in PBS (500 µg/ml) was added to each well. The Plates were incubated at 37 °C for 3 hours. The MTT product, formazon, was dissolved in 100 µl of DMSO and optical density (OD) was read by ELISA at 570 nm. The cell viability in each group was defined as a percentage of untreated control cell viability. Based on cell viability data, the IC_{50} value was estimated by linear regressive with Microsoft excel software.

2.5. Measurement of cell apoptosis

Annexin-V FITC/propidium iodide double-staining method (V-FITC/PI) is a sensitive method for the detection of quantitative apoptosis. In a 6-well plate, the SW1116 and SW48 cells were incubated for 24 hours to be attached to the plate bottom. The cells were then treated separately with Lip-Sol, CUR-Sol, CUR-Lip, HPE-Sol, HPE-Lip and HPE/CUR-Lip in fresh medium for 24 hours and re-incubated.

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After incubation, SW1116 and SW48 cells were washed three times with PBS, followed by trypsinization and cell collection. The collected cells were centrifuged at 1500 rpm for 5 min and suspended at 500 µl of PBS. Next, the cells were washed once in the 1X binding buffer and re-suspended in the 1X binding buffer, 5 µl of Annexin-V was added to 100 µl of cell and incubated for 10-15 minutes at room temperature. The cells were washed in 1X Binding Buffer and suspended in 200 µl of 1X Binding Buffer. Finally, 5 µl of Propidium Iodide staining solution was added. The cells were subsequently analyzed by flow cytometry.

2.6. Statistical analysis

Data were reported as mean ± standard deviation and statistical analysis was performed by analysis of variance (ANOVA) and Tukey's honestly significant difference (HSD) post hoc test using GraphPad Prism Version 5 software (San Diego, California, USA) at a significance level of $P < 0.05$. Also, Combenefit and Compusyn software were used to explore the effects of synergism and pharmacodynamics of the studied compounds, respectively.

3. Results

3.1. In vitro cytotoxicity and synergistic effect of HPE/CUR-Lip on SW1116 and SW48 cells

SW1116 and SW48 cell viability in all formulations was dose- and time-dependent ($P < 0.05$). The cytotoxic effect of the liposomal form of the compounds on SW1116 and SW48 cells was significantly higher than the free form of the compounds at the same concentration. These results suggest that the liposomal form is more suitable for increasing the cytotoxicity of the compounds in these cancer cells ($P < 0.05$). Nanoliposomes alone had no cytotoxic effect against CRC cell lines of SW1116 and SW48 ($P < 0.01$). The IC_{50} values of compounds are shown in Table 1. Compared with mono-drug formulations of CUR-Lip and HPE-Lip, the combination of HPE and CUR in liposomal formulation (HPE/CUR-Lip) showed the greatest cytotoxic effect. This formulation was able to significantly increase the anti-cancer effect synergistically ($P < 0.05$). SW48 cell line showed more resistance than SW1116 cell line, which was not statistically significant. Cell survival rates are shown in Fig. 1 and 2.

Table 1. The values of IC_{50} of different treated groups after 24, 48, 72h.

Cell Line	IC_{50} (µM)	CUR-Sol	CUR-Lip	HPE-Sol	HPE-Lip	HPE/CUR- Lip
SW1116	24 h	42.968	27.198	92.192	48.237	25.241
	48 h	37.812	26.657	67.338	28.817	12.624
	72 h	30.255	25.252	43.409	21.406	5.002
SW48	24 h	47.312	38.332	94.689	44.534	29.356
	48 h	44.868	34.514	65.088	38.685	19.255
	72 h	36.210	41.009	51.516	28.585	10.075

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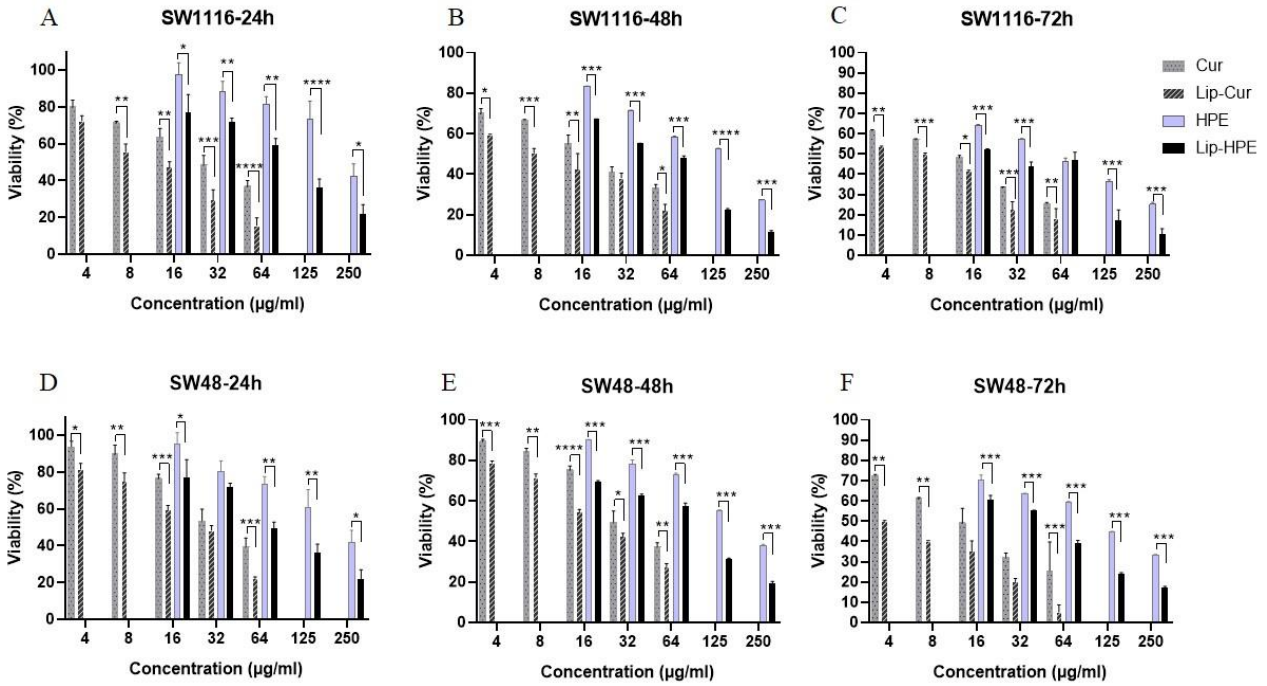


Fig. 1. The effects of different concentrations of Cur or HPE and liposomal form on the cell viability of SW1116, SW48 cells at 24 h, 48 h and 72 h times. Cell proliferation was determined by MTT assay and expressed as percentage of viable cells of treated samples to control samples. (n=3 and mean ± SD), (*P < 0.05, ** P < 0.01, *** P < 0.001, **** P < 0.0001 when comparing two similar concentrations).

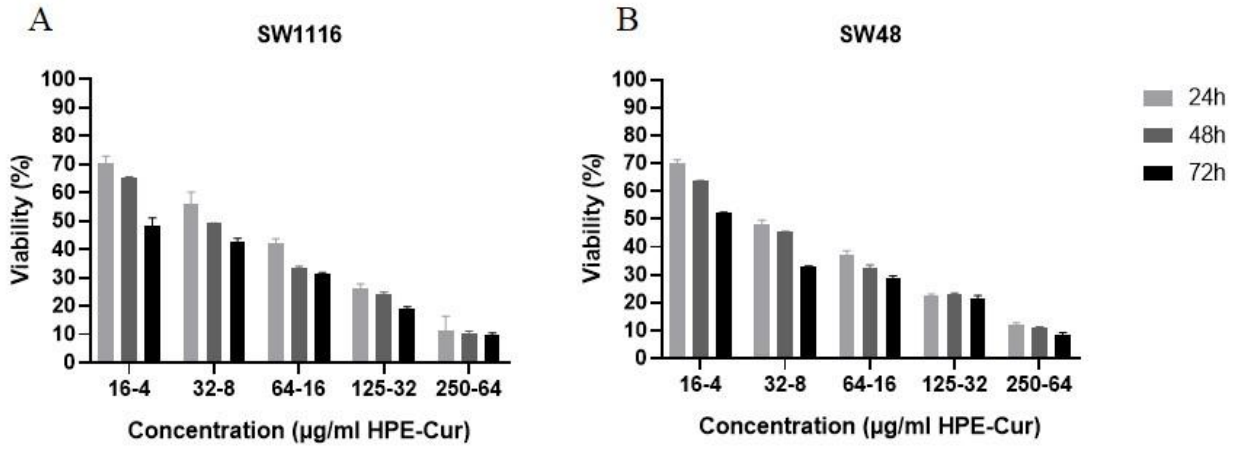


Fig. 1. *In vitro* cytotoxicity analysis combination of HPE/Cur Lips on SW1116, SW48 cell lines at 24 h, 48 h and 72 h times. Cell proliferation was determined by MTT assay and expressed as percentage of viable cells of treated samples to control samples. (n = 3 and mean ± SD)

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3.2. Cell apoptosis

The results of apoptosis in SW1116 and SW48 cell lines by CUR-Sol, CUR-Lip, HPE-Sol, HPE-Lip, HPE/CUR-Lip, Lip-Sol and control stained by V-FITC/PI are shown in Figure 3 and 4. The population of apoptotic cells treated with drug concentration increased significantly compared to the apoptosis rate in untreated cells ($P < 0.01$). The cells treated with liposomal compounds showed more significant apoptosis than cells treated with free form compounds and control group. Due to the concentration close to IC_{50} value of used compounds, the highest percentage of increase in apoptosis in SW48 and SW1116 cell lines compared to untreated control cells and nanoliposomes is related to HPE/CUR-Lip. The apoptosis rate and necrosis are shown in Figure. The percentage of apoptosis obtained from treated cells is reported in Table 2.

Table 2. Precentage of apoptosis formed after treatment with different of groups on SW1116, SW48 cell lines at 24h.

Cell Line	CUR-Sol	CUR-Lip	HPE-Sol	HPE-Lip	HPE/CUR- Lip
SW1116	30.4	31.8	39.8	42.9	56.3
SW48	18.9	21.2	36.4	45	48.8

4. Discussion

Finding new cancer therapies has become increasingly important because of many side effects and problems associated with common treatments for human cancers [5]. The administration of extracts and compounds derived from medicinal plants has received much attention due to the toxic effects of chemotherapeutic agents in the treatment of various types of cancer [21]. The present study investigated the anti-proliferative and anti-apoptotic effects of hydroalcoholic extract of HP plant alone and in combination with curcumin as monodrug form and dual drug-loaded nanoliposomes on CRC cell lines of SW1116 and SW48. In this study, first MTT colorimetric assay was used to evaluate the viability percentage of SW1116 and SW48 cells.

The results showed that CUR, HPE and nanoliposomal forms had significant cytotoxic effects on SW1116 and SW48 cancer cell lines compared to controls. The anti-proliferative activity increases when HPE and CUR are loaded on nanoliposomes. Several studies have examined the inhibitory effect of HPE as well as its effective compounds on several cell lines, including human leukemia cell line K562 [15], bladder cancer cell line T-24 [22], esophageal cancer cell line KYSE30 [23], acute myeloid leukemia cell lines NB4 and HL-60 [24], colon cancer cell line CaCo-2 [12], breast cancer cell line MCF-7 [25], glioblastoma multiform cell line U87MG [26] and liver cancer cell line HepG2 [27]. The results showed that the HPE alone had growth inhibitory and anti-proliferative effects on the mentioned cell lines, consistent with the present study. Although the above studies did not examine SW48 and SW1116 cell lines, the results indicated the anti-proliferative effects of HPE on cancer cell lines. In addition, the results of cell treatment after 48 and 72 hours showed that the HPE also inhibited cell proliferation time-dependently in both cell lines, which is consistent with a study by Ferguson et al. (2011) who found that the HPE dose-dependently and time-dependently prevented the proliferation of CRL2539 murine mammary carcinoma cell [28].

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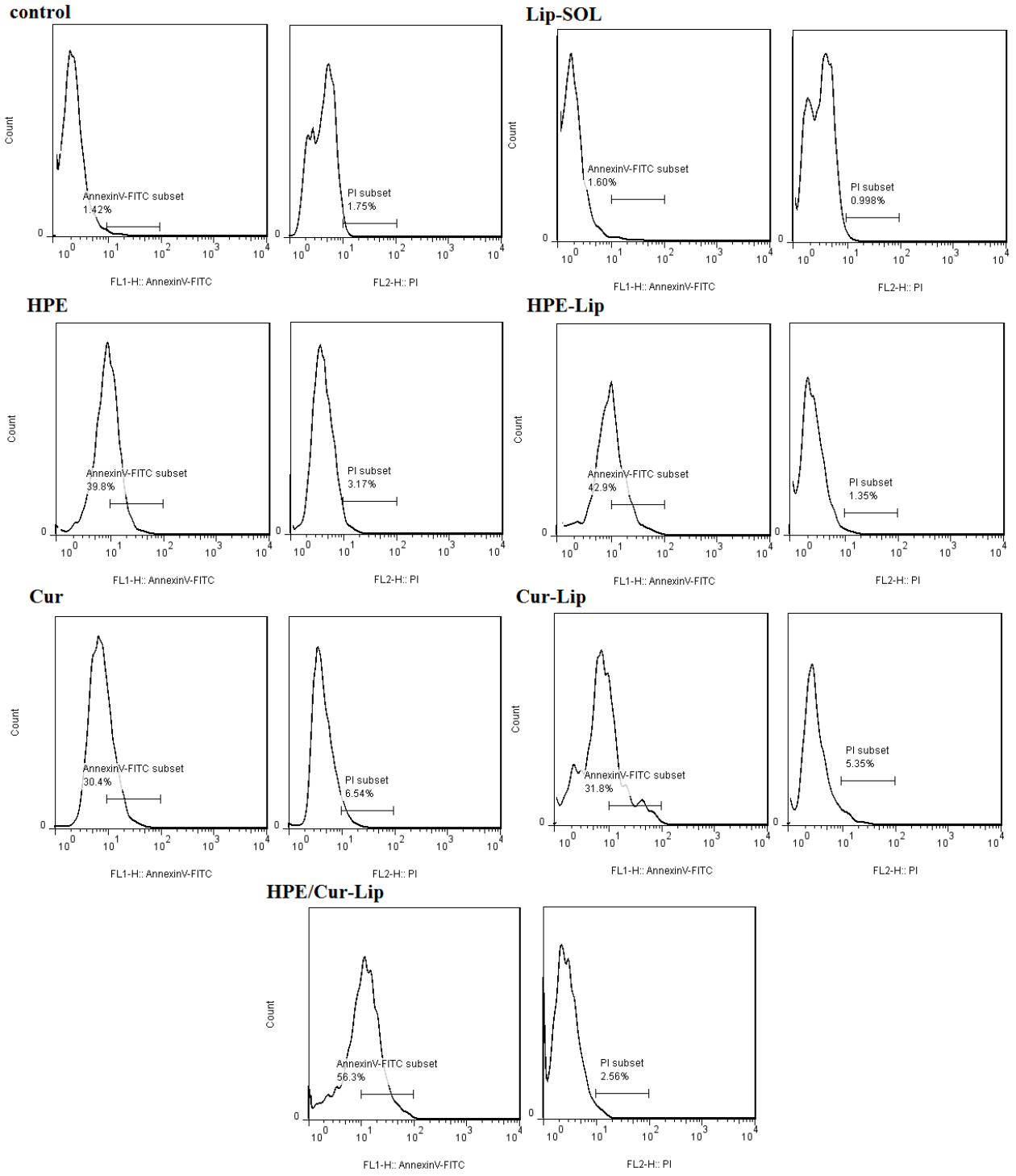


Fig. 2. Effect of different groups on apoptosis in SW1116 cells, as determined using double staining with FITC-Annexin V/PI.

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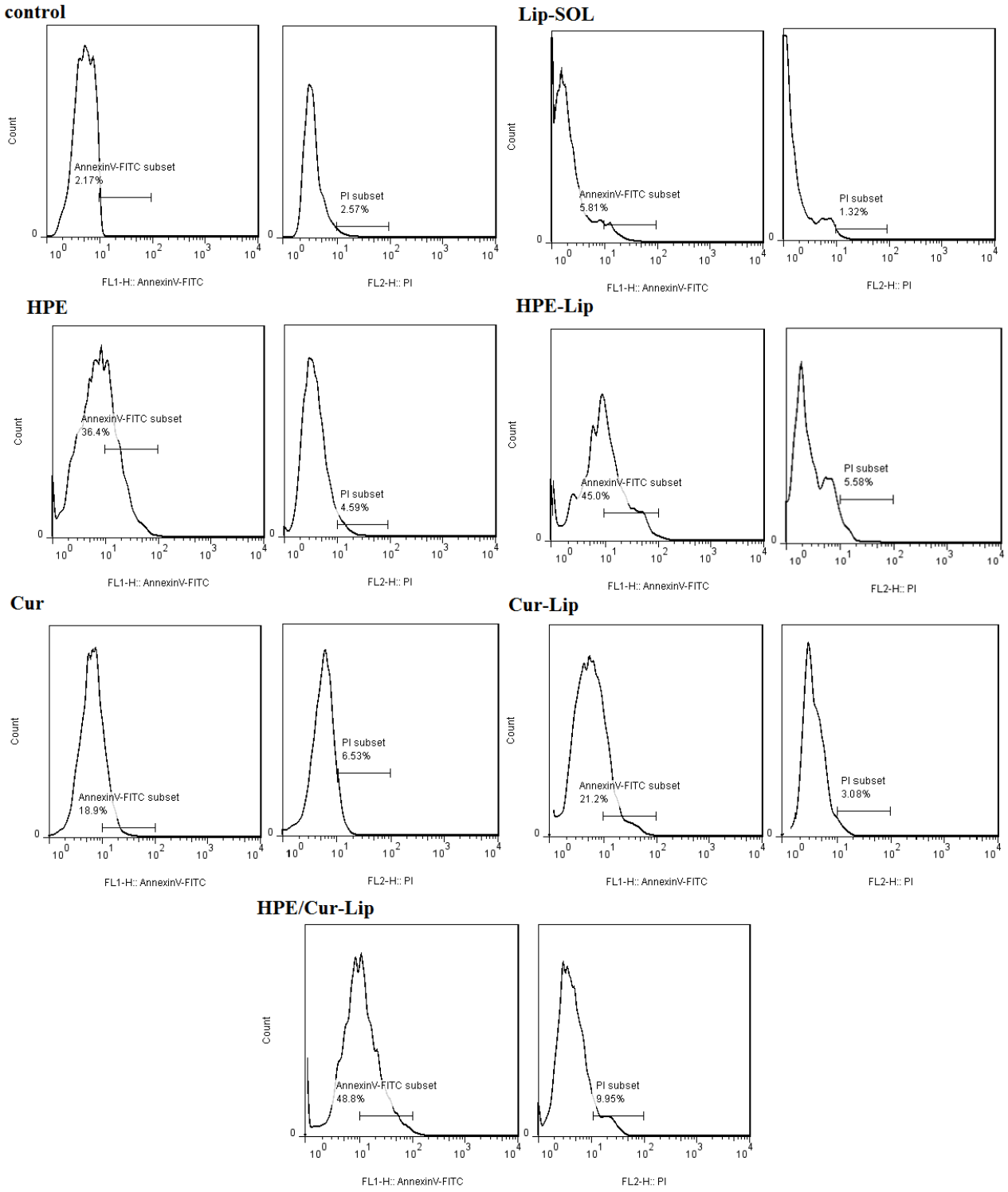


Fig. 3. Effect of different of groups on apoptosis in SW48 cells, as determined using double staining with FITC-Annexin V/PI.

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The HP plant contains several known active compounds such as hypericin, hyperforin and flavonoid compounds (e.g. kaempferol, quercetin and rutin) [26]. This plant also has antioxidant potential that can be attributed to its phenolic compounds [29]. Further studies are suggested to analyze the exact concentration of the components in the hydroalcoholic extract of HP so that the anti-proliferative effects of this extract can be definitively attributed to a specific group of substances in the extract. Similar studies, however, mainly attribute this role to hypericin, hyperforin and flavonoid compounds present in this extract [30].

On the other hand, Jain et al. stated that the toxicity of HPE does not depend only on hypericin and hyperforin and that the effect of total HP extract is greater than that of pure compounds. Hypericin and hyperforin are rich in total extract and inhibit the growth of HT-29 CRC cells [31]. Valletta et al. (2018) explicitly supported this hypothesis and stated that agents other than hypericin and hyperforin produced in total extract at different times have potent anticancer activity [15].

The CUR is a non-toxic natural bioactive compound derived from the rhizome of the turmeric plant, and has been shown to prevent the proliferation of cancer cells and has anti-tumor and anti-apoptotic activity. In the present study, the CUR also showed antiproliferative activity on cancer cells [32, 33]. In the present study, the anti-proliferative effects of these two compounds were first investigated. Most anti-cancer agents exert their therapeutic effects by inducing apoptosis [34] which is one of the most important methods in the uncomplicated elimination of cancer cells [35]. In order to confirm that the death of these cells was induced in the apoptotic pathways, the apoptotic effects of HPE and CUR were examined by staining the cells via V-FITC/PI method. In the present study, according to the results of flow cytometry analysis of cell apoptosis rate, it was shown that the HPE and CUR compounds cause loss of asymmetry of membrane phospholipid and membrane processes associated with apoptosis in a dose-dependent manner. It is caused by the externalization of phosphatidylserine (PS) and morphological changes in cell size and granulation. Consistent with the results of the present study, it has been shown that the HPE-induced apoptosis has been associated with increased caspase activity [30]. The compounds in HPE have been proven to function similarly to cisplatin, increasing p53 expression and decreasing bcl2 expression [25]. The p53 suppresses transcription of anti-apoptotic genes such as bcl2. The apoptosis is also induced in response to many DNA-damaging agents, usually by altering the expression of bcl2 family genes [36]. In addition, another study reported that the HPE alone inhibited DNA synthesis and arrested G_0/G_1 cell cycle and significantly reduced the percentage of cells in the S and G_2 phases [15], in line with the results of the present study. The anti-cancer effects of CUR on CRC cells are widely known, which is associated with activation of the apoptotic pathway [20]. Extensive studies on the underlying mechanism of apoptosis by CUR in CRC have reported several molecular targets, including enzymes such as COX-2 [37], SOD and ROS [38], transcription factors (such as catenin, NF-κB, AP-1 and PPAR-γ) [39, 40], members of the Bcl-2 family, BH3 protein (such as Bim, Bad and Bid) [41], protease enzymes (such as caspase 3 and caspase 8), death receptors (such as DR5 and Fas) and other important signaling pathways such as p53, phosphoinositide-3 kinase/protein kinase-B (PI3K/Akt), JNK and ER stress [42]. It should be noted that cancer progression is a

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multiphase, multi-gene and multi-factor process. Thus, the anticancer effects of each compound depend on the nature and number of cells and the cellular and molecular events by which the compound is regulated. Therefore, further studies are needed to determine the exact pathway of apoptosis induced by HPE and CUR nanoliposome.

The main purpose of our study was to investigate whether the combination of HPE and CUR enhances the anti-cancer effect or, conversely, causes negative interactions and adverse effects. The data showed that the inhibition of CRC cell growth after co-treatment with HPE and CUR was significantly higher compared to these two extracts alone. Similar to our study, the anti-proliferative effects of Propolis and HP in combination on U87MG glioblastoma cells were investigated and it was found that the two show greater effects in combination [26]. In another study, the HP essential oil was found to synergistically enhance the anti-cancer effects of methotrexate on MCF-7 cancer cell line [43]. These studies provide evidence that HP can improve the chemical sensitivity of cancer cells to chemotherapy drugs by regulating a variety of signaling pathways. On the other hand, the anti-cancer effect of *Cassia auriculata* leaves in combination with CUR was investigated and it was shown that the combination of the two can synergistically induce apoptosis through mitochondrial pathways [44]. Cheng et al. co-loaded cisplatin and CUR into the liposome and stated that their combination in liposomal form is a potential strategy to achieve the synergistic effect of cisplatin and CUR for the treatment of hepatocellular carcinoma [10]. Another study examined the effects of curcumin/paclitaxel-loaded liposomes, the results of which indicated that such loading and delivery systems could be used as a promising treatment to improve clinical outcomes against various malignancies [45].

Chemotherapy is widely accepted, even for metastatic malignant tumors, but the continued administration of anticancer drugs can lead to severe physical toxicity. To improve treatment with anticancer drugs and reduce their toxicity, the drug delivery systems were considered for direct delivery of drugs to the target site [46]. In this regard, the important point in this study is to improve the anti-proliferative activity of HPE and CUR by loading on nanoliposomes. This increase in effect in the form of nanoliposomes is due to the special properties of nanoliposomes; for example, this system prevents drug destruction. Therefore, it reduces the need for higher doses of the drug and repetition. The nanoparticles can interact with the cell surface a thousand times more than the drug. Because HPE and CUR have hydrophobic nature, and their systemic administration is difficult, the nanoparticles can increase the solubility and stability of existing compounds, enhance their absorption, protect their premature degradation in the body, and prolong circulation time. In addition, nanoparticles cause high absorption of the drug in the target tissue, which reduces cytotoxicity [47]. In the present study, the nanoliposomes were used to increase the anti-proliferative and anti-apoptotic potentials of HPE and CUR at the same concentrations. Although this study was performed in an *in vitro* condition, the results showed more effects of the extract when loaded to nanoparticles. Consistent with the present study, (Pradeep et al., 2019) investigated the antioxidant and anti-inflammatory effects of hypericin-rich *Hypericum hookerianum* extract liposome on fibroblasts. Their results indicated that hypericin-rich plant extract's liposome could be a useful source for new antioxidant and anti-

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inflammatory compounds [48]. Another study showed that HPE-loaded polylactic acid (PLA) nanoparticles exhibited higher photoactivity than the free drug in the NuTu-19 epithelial ovarian cancer cell line [49]. The results of these studies are consistent with the present study. As for the CUR, the liposomal form has been shown to penetrate cancer cells more easily [19]. These findings indicate the positive effect of nanoliposomes on drug delivery mechanism. Therefore, using nanoliposomes is a suitable strategy to improve the therapeutic properties of cytotoxic drugs.

5. Conclusion

The current study aimed to synthesize the HPE/CUR-co-loaded liposomes. These liposomes can increase synergistically *in vitro* cytotoxic and apoptotic effects of HPE and CUR in the treatment of CRC. Subsequently, loading the HP active ingredient with CUR into the nanoliposome could establish an effective pathway to overcome the potential for proliferation and induction of apoptosis in colorectal cancer cells, as well as to investigate the molecular mechanisms involved in inhibiting proliferation and inducing apoptosis. In addition, other extensive studies can be designed, including the use of animal models, to clearly determine the effectiveness of combination therapy.

Author contributions

FR: writing original draft, performed experiments, conceptualization, investigation, formal analysis, visualization. HB: investigation, conceptualization, formal analysis. FG, FJ, SH: conceptualization, formal analysis. GG: conceptualization, writing original draft, review & editing, supervision, project administration, funding acquisition. All authors agree to be accountable for all aspects of work ensuring integrity and accuracy. All data were generated in-house, and no paper mill was used.

Conflict of interest

The authors have declared no conflict of interest.

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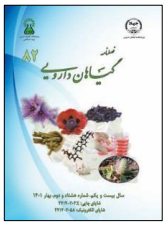
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مقاله تحقیقاتی

اثر پروآپوپتوتیک نانولیپوزوم‌های بارگذاری شده با عصاره هیدروالکلی گل راعی در ترکیب با کورکومین بر رده‌های سلولی سرطان کولورکتال SW48 و SW1116

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اطلاعات مقاله

گل‌واژگان:
گل راعی
کورکومین
نانولیپوزوم
سرطان کولورکتال
آپوپتوز

چکیده

مقدمه: سرطان کولورکتال (CRC) همچنان یکی از علل اصلی مرگ و میر ناشی از سرطان در جهان است و تقریباً ۷۰ تا ۷۵ درصد از بیماران مبتلا به سرطان کولورکتال متاستاتیک تا ۱ سال پس از تشخیص زنده می‌مانند. کورکومین (CUR) یک عامل شیمی درمانی بالقوه است که برای درمان سرطان استفاده می‌شود. شواهد زیادی از اثرات بازدارنده عصاره گل راعی (*Hypericum perforatum* extract: HPE) بر تکثیر سلولی و اثرات آن بر القای آپوپتوز در رده‌های سلولی مختلف سرطان انسان وجود دارد. **هدف:** هدف از این مطالعه بررسی اثر پروآپوپتوتیک HPE و نانولیپوزوم‌های آن (HPE-Lip) و بررسی پتانسیل هم‌افزایی و درمانی ترکیب نانولیپوزوم آنها (HPE/CUR-Lip) بود. **روش بررسی:** در مطالعه آزمایشگاهی حاضر، رده‌های سلولی SW1116 و SW48 کشت و سپس با دوزهای مختلف HPE، CUR، لیپوزوم تنها (Lip-Sol) و نانولیپوزوم‌های بارگذاری شده با HPE (HPE-Lip)، CUR (CUR-Lip) و CUR/HPE (HPE/CUR-Lip) به مدت ۲۴، ۴۸ و ۷۲ ساعت تیمار شدند. سمیت سلولی با روش MTT و میزان آپوپتوز با روش رنگ‌آمیزی یدید پروپیدیوم انکسین-V با استفاده از فلوسیتومتری اندازه‌گیری شد. **نتایج:** نتایج نشان داد که زنده مانی سلولی در تمامی گروه‌ها به صورت وابسته به دوز و زمان در مقایسه با گروه کنترل مهار شد. استفاده از نانولیپوزوم‌ها نتایج را بهبود بخشید. HPE/CUR-Lip فعالیت سیتوتوکسیک و پروآپوپتوتیک بیشتری در شرایط آزمایشگاهی در برابر رده‌های سلولی سرطان روده SW1116 و SW48 نشان داد ($P < ۰/۰۵$). **نتیجه‌گیری:** یافته‌های این مطالعه نشان می‌دهد که کمپلکس HPE/CUR-Lip می‌تواند یک استراتژی بالقوه برای دستیابی به اثر هم‌افزایی HPE و CUR در درمان سرطان کولورکتال ارائه کند.

مخففها: ANOVA، آنالیز واریانس یک‌طرفه؛ AP-1، پروتئین فعال کننده ۱؛ Bcl-2، لنفوم سلول B 2؛ JNK، کیناز متصل شونده به کربن در پایانه نیتروژنی؛ CRC، سرطان کولورکتال؛ Cox-2، سیکلواکسیژناز-۲؛ CUR، کورکومین؛ DMSO، دی متیل سولفوکسید ؛ DSPC، دی استئاروئیل فسفاتیدیل کولین؛ FBS، سرم جنین گاوی؛ FITC، فلورسئین ایزوتیوسیانات؛ IC_{50}، غلظت مهارکنندگی متوسط؛ HSD، اختلاف معنی‌دار صادقانه؛ HPE، عصاره گل راعی؛ Lip، نانولیپوزوم؛ MTT، ۳-(۵،۴)- دی متیل تیازول-۲-ایل)-۵،۲- دی فنیل-۲-H-تترازولیوم بروماید؛ NF-κB، عامل هسته ای کاپا B؛ PBS، نمک فسفات بافر؛ PS، فسفاتیدیل سرین ؛ PI3K،PI3K/AKT ، فسفوئینوزیتید-۳ کیناز/پروتئین کیناز-B؛ PI، پروپیدیوم یدید؛ PLA، پلی لاکتیک اسید؛ PPAR-γ، گیرنده گامای فعال شده با تکثیر کننده پراکسی زوم؛ ROS، گونه‌های اکسیژن واکنش‌پذیر؛ SOD، سوپراکسید دیسموتاز

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