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Candida albicans cell-free extract against human gastric cancer; an *in-vitro* study

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Abstract

Objective Yeast cell-free extracts and supernatants contain several compounds such as β-glucan, mannan, chitin, and mannoprotein with potent antitumor and other health-promoting activities. Candida albicans have been frequently and widely isolated from different habitats compared to other yeasts. The supernatant extracted from this yeast also contains β-glucan, chitin, and mannan compounds. This study investigates the anticancer, apoptosis-inducing, and downregulation of proinflammatory gene expression activities in normal and drug-resistant human stomach cancer cells (EPG and RDB cell lines) after 24 and 48 h treatment.

Results We found that *Candida albicans* supernatant-induced apoptosis suppressed the *survivin* gene expression in both cell lines and suppressed the expression of *IL-8* and *NF-κB* genes in normal stomach cancer cells. IC_{50} for EPG cells were 1599 µg/mL and 1040 µg/mL after 24 and 48 h treatment, respectively; and for RDB cells were 877 µg/mL and 675 µg/mL after 24 and 48 h treatment, respectively. Consequently, this work suggests that *Candida albicans* supernatant can potentially protect against and treat human stomach cancer.

Keywords Human stomach cancer, *Candida albicans*, Yeast cell-free extract, Anticancer activity

Introduction

Gastric cancer is one of the most important and widespread deadly global diseases, with seriously poor overall survival statistics worldwide. It is the second leading cause of cancer death worldwide, affecting more than one million people annually [1]. It is recently estimated that the global incidence and mortality rates for gastric cancer disease are 11.1 and 8.2 per 100,000 persons in both men and women, respectively [2]. With increasing age, the incidence rate of gastric cancer also increases. However, this chronic disease is multifactorial. Several interacting environmental and genetic factors such as family history, diet, smoking, alcohol consumption, *Helicobacter pylori*, and *Epstein-Barr virus* infections can significantly influence its development [3]. Several adverse symptoms and severe side effects of anticancer and treatment strategies have been reported in patients. Therefore, scientists worldwide are encouraged to seek alternative cancer treatment and prevention strategies. So far, different natural plant and microbial-based compounds have been extracted, developed, evaluated, and presented as potential for treating and preventing various human cancers. The most negligible side effects and adverse symptoms have been observed for these treatment strategies [4–6].

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Researchers have employed cell-free supernatant and metabolic compounds released from probiotic bacterial and fungal strains, including *lactic acid bacteria*, *Enterococcus faecalis*, *Kluyveromyces marxianus*, and *Saccharomyces boulardii* as potential antimicrobial and antitumor agents against different foodborne pathogens and human cancer cell lines, respectively [7–11]. *Candida* is one of the most important fungal pathogens causing human mycoses and superficial mucosal diseases. However, several functional compounds, such as mannoprotein and different bioactive peptides, have been recognized in cell-free supernatants released from this pathogenic yeast [12–14]. So far, the antitumor activity of *Candida* cell-free extracts has not been investigated. Therefore, in this study, we aimed to study the anticancer and apoptosis-inducing properties of *C. albicans* supernatant (CAS) against human gastric cancer cells.

Main text

Fungal strain and CAS preparation

Lyophilized *C. albicans* PTCC 5027 was purchased from the Iranian Research Organization for Science and Technology (IROST), Persian Type Culture Collection, Tehran, Iran, and used in this study. Yeast cell-free supernatant was prepared according to the method previously described by Fortin et al. (2018). *C. albicans* cells were grown in Sabouraud solid medium (Oxoid, UK) at 30 ˚C for 72 h. CAS was separated using centrifugation at 7000 rpm for 15 min and passing through a 0.22-µm membrane filter [11]. CAS was freeze-dried and diluted in 500, 1000, 1500, 2000, and 2500 µg/mL concentrations with cell culture medium supplemented with antibiotics and FBS to treat colon cancer cells.

Cancer cell line and CAS treatments

Normal and drug-resistant human gastric cancer cell lines, including EPG85-257P (EPG) and EPG85-257RDB (RDB), respectively, were purchased from the Pasteur Institute (Pasteur In., Iran) and used in this study as the cell models. All cell lines were activated by culturing in RPMI 1640 medium supplemented with antibiotics (100 µL/mL streptomycin and 100 µL/mL penicillin) and 10% (v/v) FBS with incubation at 5% CO_2 and 37 °C. Subcultures of the stock EPG and RDB cell lines were prepared for anticancer treatments by culturing into the 96-well microplates at 80% confluence. After the cell monolayer formation in each well, cell lines were treated with different concentrations of CAS. Standard dimethylsulfoxide (DMSO) was used as the control treatment in this study. Treated cells and control samples were harvested for cell viability assessment, measurement of relative gene expression, and cell apoptosis analysis after 24 and 48 h.

Cytotoxicity assessment

Cell viability of stomach cancer cells was evaluated using an MTT assay [15]. The 96-well microplates containing treated cell lines were renewed with RPMI 1640 cell culture medium containing 0.5 mg/mL MTT. Microplates were incubated at 5% CO_2 and 37 °C for 4 h. RPMI medium was discarded, dimethyl sulfoxide (DMSO) was replaced into each well and the colour changes were measured at 570 nm by using a microplate reader model Elx808 (BioTek, USA).

Flow cytometry for cell apoptosis evaluation

The BD FACS-Calibur flow cytometry machine (Dickinson Immunocytometry system, CA, USA) and EbioScience cell apoptosis kit (Ebioscience, San Diego, USA) containing Annexin V-FITC and propidium iodide (PI) staining were used to evaluate apoptosis in EPG and RDB cells. According to the kit manufacturer's instructions, 10^6 cells per well were seeded in a 6-well microplate, treated with CAS in IC_{50} concentration, and incubated at 5% CO_2 and 37 °C for 24 and 48 72 h. Harvested treated and control cells were incubated with Annexin V-FITC and PI for 30 and 5 min at room temperature in a dark place. The fluorescence of PI and annexin were measured using the flow cytometry instrument.

Survivin, IL-8, and NF-ƙB gene expression

This study measured the expression of *survivin*, *IL-8*, and *NF-ƙB* mRNA to evaluate the anticancer effects of CAS against EPG and RDB cells using reverse transcriptase real-time PCR and $2^{-\Delta\Delta Ct}$ methods. According to manufacturers' instructions, total RNA was extracted using the commercial RiboEx total RNA extraction kit (GeneAll Biotechnology Co., Korea). cDNA was then synthesized using the total extracted RNA, GeneAll cDNA synthesis kit (GeneAll Biotechnology Co., Korea), and ABI PCR thermal cycler model 9092 (Applied biosystems, USA) according to the kit instructions. Real-time PCR was carried out using the Ampliqon qRT-PCR SYBR green master mix (Ampliqon, Denmark) and the RotorGene real-time PCR machine model 6000 (QiaGen, USA). GAPDH (Glyceraldehyde 3-phosphate dehydrogenase) primers also were used as the internal control. PCR amplification for proinflammatory and *survivin* gene expression was performed according to the primers and thermal cycling procedures described in detail [8, 16–18]. Relative gene expressions were measured after the calculation of the cycle threshold (C_t) for each reaction by using the $2^{-\Delta\Delta Ct}$ method as previously described by Osakabe et al. (2017) [19].

Statistical analysis

Analysis of variance (ANOVA) was employed to determine significant ($P<0.05$) differences among variables by

using SPSS version 23.0.0 (SPSS Inc., Chicago, IL, USA). All experiments and measurements were carried out in triplicates.

Results

This study investigated the cytotoxic potential of cell-free extract obtained from *C. albicans* against normal and drug-resistant stomach cancer cells. Figure 1A and B demonstrate the cell viability of EPG (IC_{50} 1599 µg/mL and 1040 µg/mL after 24 and 48 h, respectively) and RDB (IC_{50} 877 µg/mL and 675 µg/mL after 24 and 48 h, respectively) cell lines, respectively treated with different concentrations of CAS after 24 and 48 h. Significant ($P<0.05$) reductions in cell viability were found in EPG and RDB cell lines treated with various concentrations of CAS. Notably, a dose-dependent and time-dependent decrease in cell viability of both normal and resistant drug stomach cancer cells was observed.

Apoptosis induced in EPG and RDB cells treated CAS at IC_{50} concentrations after 24 and 48 h are shown in Fig. 2B-C and E-F, respectively. To calculate the total apoptotic cell proportion, proportions of late (Q2) and early (Q3) apoptosis in each treated cell line were added to each other (Q2 + Q3). According to Fig. 2A-C, total apoptotic cell proportions of control and normal stomach cancer cells treated with CAS at IC_{50} concentration after 24 and 48 h were calculated at 8.62, 30.65, and 36.52%, respectively (Table 1). The proportions of total

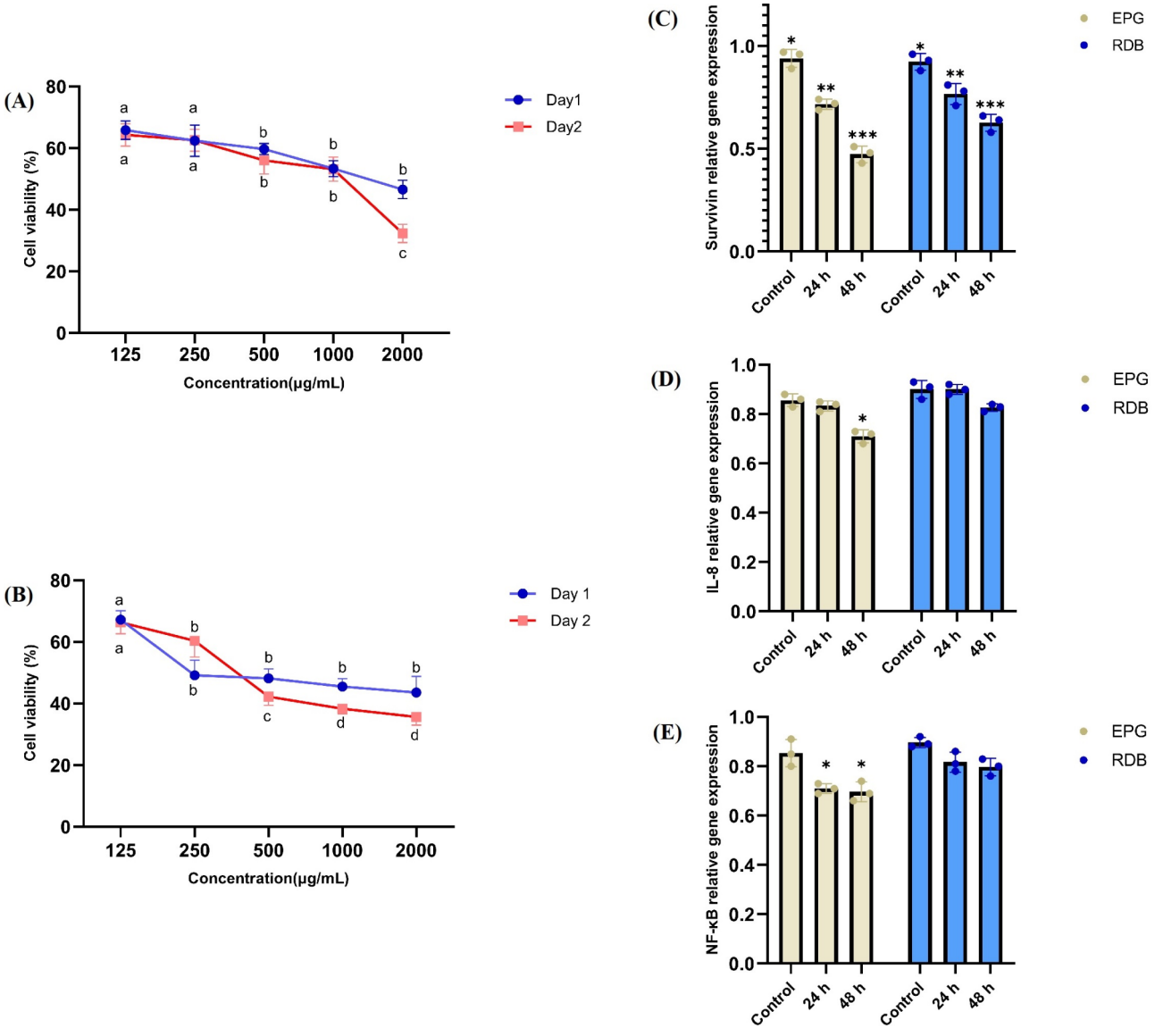

Fig. 1 Cell viability of EPG (**A**) and RDB (**B**) cells under exposure to different concentrations of CAS after 24 and 48 h evaluated by using the MTT method. Relative gene expression of *surviving*, (**C**) *IL-8* (**D**) and *NF-ƙB* (**E**) genes in EPG and RDB cells treated with CAS. Alphabetical letters indicate significant differences ($P<0.05$). *,** and *** indicate significant ($P<0.05$) differences

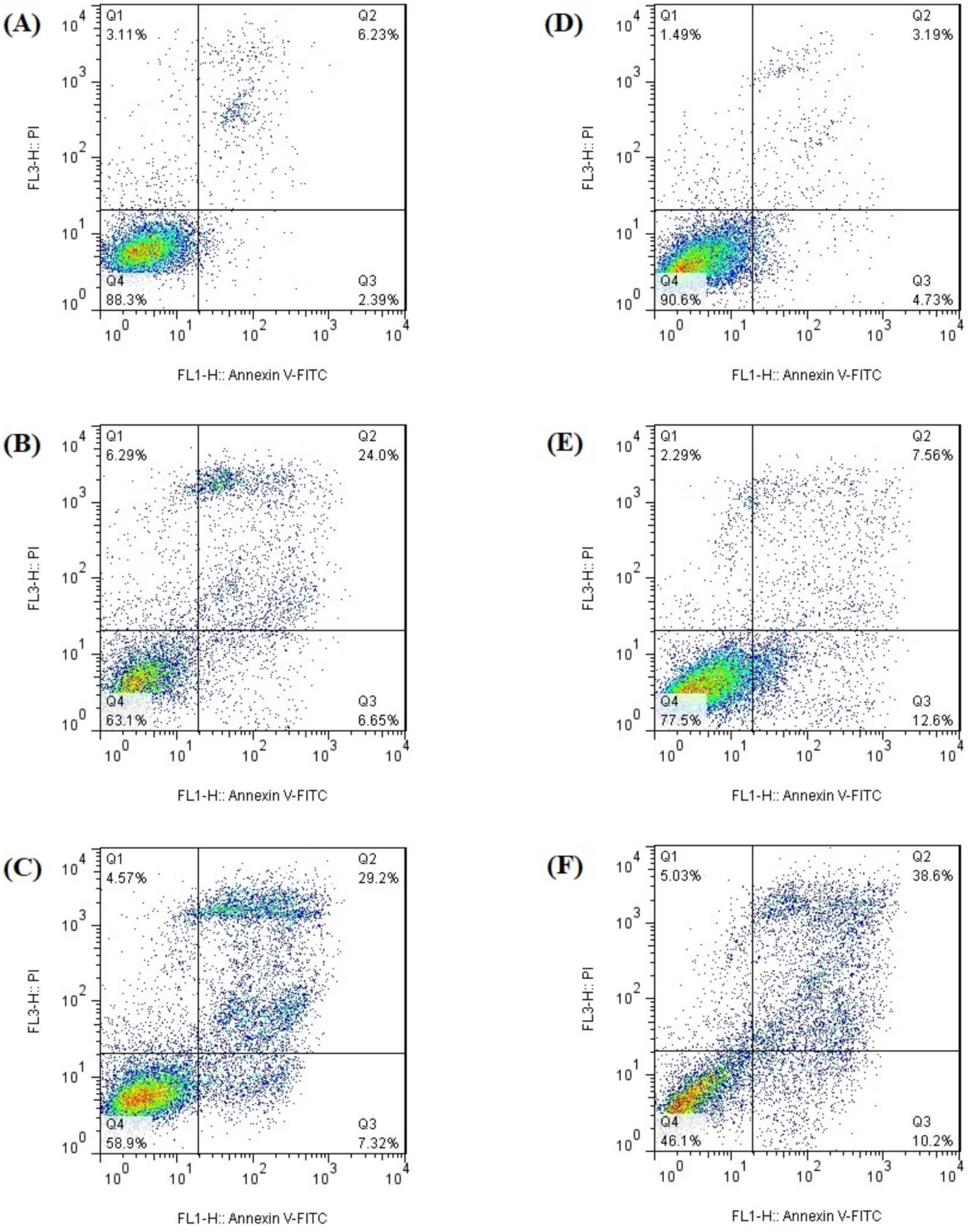

Fig. 2 Apoptotic analysis of EPG cells treated with CAS using flowcytometry method. (Untreated sample (**A**), treated samples after 24 h (**B**) and 48 h (**C**)). Apoptotic analysis of RDB cells treated with CAS using flowcytometry method. (Untreated sample (**D**), treated samples after 24 h (**E**) and 48 h (**F**))

Table 1 Total apoptotic cell proportions, relative *survivin*, *IL-8* and *NFκB* gene expressions in EPG and RDB cells treated with CAS after 24 and 48 h treatment

Cell line	Time of treatment	Total apoptotic cell proportion (%)	Relative survivin gene expression	Relative IL-8 gene expression	Relative NFκB gene expression
EPG	Control	8.62 ± 2.71^{a}	0.96 ± 0.2^{a}	0.86 ± 0.4^{a}	0.85 ± 0.5^{a}
	24 h	30.65 ± 2.12^{b}	0.72 ± 0.3^{b}	0.84 ± 0.4^{a}	0.71 ± 0.3^{b}
	48 h	36.52 ± 0.94^{c}	0.48 ± 0.8^{c}	0.72 ± 0.3^{b}	0.69 ± 0.2^{b}
RDB	Control	7.92 ± 1.84^{a}	0.93 ± 0.2^{a}	0.91 ± 0.3^{a}	0.88 ± 0.4^{a}
	24 h	20.16 ± 3.40^{b}	0.78 ± 0.4^{b}	0.90 ± 0.4^{a}	0.81 ± 0.3^{a}
	48 h	48.80 ± 2.83^{c}	0.64 ± 0.7^{c}	0.83 ± 0.3^{a}	0.80 ± 0.4^{a}

Different alphabetic characters (a, b and c) indicate significant differences ($P < 0.05$) in each column (for each cell line)

apoptotic cells in control and drug-resistant stomach cancer cells treated with CAS at IC_{50} concentration after 24 and 48 h were measured at 7.92, 20.16 and 48.80%, respectively (Table 1). Induced apoptosis in both normal and drug-resistant stomach cancer cells treated with CAS at IC_{50} concentrations significantly ($P < 0.05$) increased in comparison to the control cells (treated with DMSO). Because of the effects of cell aggregation in flow cytometry assay, fluctuations in proportions of necrotic cells were observed occasionally in the present study.

Relative expression of *survivin*, *IL-8*, and *NF-κB* genes in drug-resistant and normal stomach cancer cells treated with CAS at IC_{50} concentration after 24 and 48 h have been illustrated in Fig. 1C-E, respectively. The mRNA expression of the *survivin* gene was significantly ($P < 0.05$) suppressed in both normal and drug-resistant stomach cancer cells treated with CAS after 24 and 48 h compared with the control cells. *Survivin* gene expression was significantly ($P < 0.05$) more decreased after 48 h treatment than after 24 h in both cancer cells (Table 1). Expression of the *IL-8* gene was significantly ($P < 0.05$) suppressed after 48 h in normal stomach cancer cells; however, it is not significantly ($P < 0.05$) decreased in drug-resistant stomach cancer cells treated with CAS. *NF-κB* gene expression was also significantly ($P < 0.05$) decreased after 24 treatments with CAS; however, it was not significantly ($P < 0.05$) suppressed in drug-resistant cancer cells (Table 1).

Discussion

Treatment with CAS showed significant apoptosis-inducing activities in both normal and resistant cancer cell lines; however, these activities were significantly more after 48 h than after 24 h treatment compared with untreated cells in this study. Most developed anticancer agents currently used exert antiproliferative effects on cancer cells through apoptosis-inducing activity [20]. Fortin et al. (2017) studied the antiproliferative properties of polysaccharide compounds extracted from *Kluyveromyces marxianus* and *Saccharomyces boulardii* against colorectal cancer cells. They found that cell-free extracts of *K. marxianus* and *S. boulardii* exert apoptosis-inducing and growth inhibition effects in a dose-dependent manner in human colon cancer cells due to the presence of β-glucan, mannan, chitin, and mannoprotein in the cell wall of these probiotic yeasts [11]. Another research evaluated the apoptosis-inducing effects of the metabolites secreted from probiotic yeast Pichia kudriavzevii against human colorectal cancer cells in 2017 [21]. Pakbin et al. (2021 and 2022) investigated the antitumor activity of *S. boulardii* (SBS) probiotic yeast supernatant against normal and drug-resistant human stomach and breast cancer cells, and they found growth inhibitory and apoptosis-inducing activities of SBS in cancer cells [8, 22]. Allahyari et al. (2020) reported the anticancer effects of SBS as a natural product from a probiotic yeast against human colorectal cancer cells [23]. β-glucan, mannan, and mannoproteins are bioactive compounds in yeast cell walls are commonly responsible for antioxidant and anticancer activities of yeast cell-free extract and supernatant [24–27]. β-glucan, chitin, and mannan are the principal compounds in C. albicans cell wall. In this study, they might be associated with the observed growth inhibitory, apoptosis-inducing and antitumor activities of CAS in stomach cancer cells [27, 28]. However, there are specific cell wall proteins in *C. albicans* cell wall demonstrated some bioactive and functional properties [29].

Anticancer agents and compounds suppress the expression of *survivin* and proinflammatory genes in cancer cells and verify the anticancer agents' growth-inhibitory and apoptosis-inducing properties [30, 31]. In this study, we found that CAS significantly suppressed the *survivin* gene expression in both normal and drug-resistant stomach cancer cells; however, proinflammatory genes (*IL-8* and *NF-κB*) were just reduced in normal cancer cells treated with CAS. Several researchers indicated the association between the suppression of proinflammatory genes and growth-inhibitory properties of anticancer agents [32, 33]. We also observed previously the suppression of *survivin* gene expression in both human breast and stomach cancer cells treated with SBS [8, 22, 33]. Allahyari et al. (2020) also found the same results in

human colorectal cancer cells treated with SBS [23]. It has been demonstrated that specific compounds in yeast supernatant and cell-free extracts, such as mannan and beta-glucan, play a key role in inducing antiproliferative effects and apoptosis in cancer cells. These properties highlight their potential as alternative anticancer agents [22–29].

Regarding the safety concern and opportunistic pathogenicity nature of *Candida* species, Yadav et al. (2012) reviewed this yeast's biotechnological aspects and industrial exploitations. Compared with other yeasts such as *S. boulardii* and *K. marxianus*, *C. albicans* has been frequently isolated from different habitats; therefore, it can be considered a potential for yeast supernatant production, especially for anticancer treatments [28, 34]. Cell-free extract and supernatant of *C. albicans* or any other yeast is completely safe for human health [9, 11, 28, 35]. Regarding the limitations of this study, future studies for investigation of other aspects of antitumor activity of CAS, *C. albicans* cell wall extract, and metabolites against different human cancer and normal cells are highly recommended to be implemented.

Conclusions

The results obtained in this study demonstrated that the cell-free supernatant of *C. albicans* exhibited remarkable antitumor activity against normal and drug-resistant human stomach cancer cells (EPG and RDB cell lines, respectively). CAS-induced apoptosis suppressed the *survivin* gene in both cell lines and downregulated the expression of *IL-8* and *NF-ƙB* genes in normal stomach cancer cells.

Limitations

- This study showed the anticancer properties of CAS against human stomach cancer cells; however, the apoptosis-inducing impact and cytotoxicity of CAS should also be investigated on human stomach normal and non-cancerous cells for toxicity evaluation.
- We acknowledge that the inclusion of Western Blot analysis would strengthen this study by providing further validation of the gene expression methodology; therefore, this represents also a limitation of our research.

Abbreviations

CAS	Candida albicans supernatant
MTT	3-[4,5-dimethylthiazole-2-yl]-2,5-diphenyltetrazolium bromide
IC_{50}	Half maximal inhibitory concentration
DMSO	Dimethyl sulfoxide
IL-8	Interleukin 8
NF-ƙB	nuclear factor kappa B
SBS	S. boulardii supernatant

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Author contributions

Conceptualization, B.P., R.O. and S.A.; methodology, B.P., S.P.D., B.F.S., F.M. and S.A.; soft-ware, B.P. and W.M.B.; validation, A.P.; formal analysis, R.O., B.P., A.A. and F.M.; investigation, B.P.; re-sources, F.M.; data curation, B.P. and F.M.; writing—original draft preparation, B.P.; writing—review and editing, B.P. and R.O.; visualization, A.A. and A.P.; supervision, F.M.; project administration, B.P.; funding acquisition, F.M. All authors have read and agreed to the published version of the manuscript.

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Data availability

We confirm that all data supporting the findings of this research are available within the article.

Declarations

Ethics approval and consent to participate

This study was conducted in accordance with the principles outlined in the Declaration of Helsinki (http://www.wma.net/en/30publications/10policies/b3/index.html). The research protocol was reviewed and approved by the ethical committee board of the Qazvin University of Medical Science, Qazvin, Iran, approval number 2022/08/09/QUMS-400000387. All participants provided written informed consent prior to their participation in the study.

Consent for publication

Not applicable.

Competing interests

The authors declare no competing interests.

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