ANTITUMOUR EFFECT OF FEVER RANGE WHOLE-BODY HYPERTHERMIA WITH CURCUMIN IN BREAST CANCER

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DEDICATION

This thesis is dedicated to my beloved family, who has been my source of strength and inspiration through my thick and thin, who continuously provides their moral, spiritual, emotional and financial support.

To my supervisors, friends and lab mates who shared their knowledge, words of advice and encouragement to finish this study.

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ABSTRACT

Breast cancer is a complex and heterogeneous disease, and one of the major types of cancer among females worldwide. In 2011, breast cancer accounted for 32.1% (18,206) of all cancer among females in Malaysia and the prevalence has been increasing since then. Current treatments of breast cancer include surgery, radiotherapy, endocrine therapy, biologic therapy, hormone therapy, chemotherapy, thermotherapy (hyperthermia), or a combination of these regimens. Hyperthermia is the procedure of elevating the temperature of a part of or the whole body to be above normal for a definite period of time using external and internal heating devices. Curcumin is a hydrophobic polyphenol, a dietary phytochemical, and a principle active ingredient derived from turmeric. Curcumin has been traditionally used for centuries as a food additive and as active agent in traditional medication. Hyperthermia given locally or whole body is often delivered as management of breast cancer besides chemotherapy. Even though chemotherapy provides survival advantages for many women with breast cancer, there are probable adverse effects and toxicity to the patients treated with chemotherapy. Due to the severe side effects of chemotherapy and the elevated death rate related to cancer, many cancer patients seek for complementary and alternative medicines (CAM), comprised of natural herbal medicines and plants as a method of treatment. Thus, this research was conducted to combine hyperthermia with curcumin as an alternative treatment of breast cancer. The effects of a combination treatment consisting of whole-body fever-range hyperthermia with curcumin on tumour growth were examined in this study. BALB/C mice were inoculated with EMT6 breast cancer cells subcutaneously and assigned to four treatment groups: (i) untreated (control), (ii) orally curcumin (50mg/kg body weight) (CUR), (iii) twice fever-range whole-body hyperthermia 39.0°C (± 0.5) for 15 minutes (FRWBH), (iv) orally curcumin (50mg/kg body weight) and twice fever-range whole-body hyperthermia 39.0°C (± 0.5) for 15 minutes (FRWBH+CUR). Following the treatment, mice body weight and tumour volume were measured throughout 28 days of experiment. The hematological parameters such as hemoglobin (Hb), platelet (PLT), red blood cells (RBC), white blood cells (WBC), lymphocytes (LYM) and neutrophils (NEUT), platelet – lymphocyte ratio (PLR) and neutrophil-lymphocyte ratio (NLR) were investigated at the end of experiment (day-28). Median survival time was determined for each group. The results presented that the tumour growth inhibition in combination treatment (FRWBH+CUR) was 82.91% with a significant difference ($p=0.0440$) compared to control. Mice treated with FRWBH+CUR had the longest median survival time which was 42 days. FRWBH+CUR treatment was well tolerated and safe to the mice with significance difference in percentage body weight gain was observed compared to control ($p=0.001$) up to 28 days of experiment. Even though there was frequent occurrence of the normal complications of cancer such as anaemia and thrombocytopenia in the group that received FRWBH+CUR treatment, PLR and NLR results indicated that the combination treatment (FRWBH+CUR) give better prognosis outcome than single treatment. As a conclusion, treatment of fever-range whole-body hyperthermia with curcumin (FRWBH+CUR) exhibited good antitumour effect in breast cancer-induced mice and this treatment has the potential as an alternative treatment of breast cancer.

ABSTRAK

Kanser payudara merupakan penyakit yang kompleks, mempunyai pelbagai ciri dan merupakan salah satu jenis kanser yang utama di kalangan wanita sedunia. Pada 2011, sebanyak 32.1% (18,206) kes kanser payudara berlaku dalam kalangan wanita di Malaysia dan sejak itu prevalens kanser ini semakin meningkat. Terdapat pelbagai rawatan kanser payudara termasuk pembedahan, radioterapi, terapi endokrin, terapi biologi, terapi hormon, kemoterapi, termoterapi (hipertermia) dan gabungan antara rawatan-rawatan tersebut. Hipertermia merupakan prosedur rawatan di mana suhu sebahagian atau seluruh tubuh ditingkatkan melebihi suhu tubuh normal dalam tempoh tertentu menggunakan peralatan pemanas luaran dan dalaman. Kurkumin adalah polifenol hidrofobik, bahan fitokimia pemakanan dan merupakan bahan aktif utama yang terdapat dalam kunyit. Kurkumin digunakan secara tradisi sebagai bahan tambahan dalam makanan dan dan sebagai bahan aktif dalam rawatan tradisional. Dalam rawatan kanser payudara, hipertermia sering diberikan secara setempat atau seluruh badan di samping kemoterapi. Walaupun kemoterapi memberikan kelebihan kelangsungan hidup bagi ramai wanita yang menghidapi kanser payudara, terdapat kemungkinan kesan sampingan dan keracunan kepada pesakit yang dirawat dengan kemoterapi. Akibat kesan sampingan kemoterapi yang teruk dan peningkatan kadar kematian disebabkan kanser, semakin ramai pesakit kanser mendapatkan rawatan komplementari dan alternatif yang terdiri daripada rawatan herba asli dan tumbuhan sebagai satu kaedah rawatan. Oleh itu, kajian ini dijalankan dengan menggabungkan rawatan hipertermia bersama kurkumin sebagai rawatan alternatif kanser payudara. Kesan gabungan rawatan *whole-body fever range hyperthermia* dan kurkumin terhadap pertumbuhan tumor dikaji dalam kajian ini. Anak tikus jenis BALB/C telah diinokulasi dengan sel kanser payudara EMT6 secara subkutaneus dan telah dibahagikan kepada empat kumpulan rawatan (i) tiada rawatan (kawalan), (ii) oral curcumin (50mg/kg berat badan) (CUR), (iii) dua kali rawatan *whole-body fever range hyperthermia* 39.0°C (± 0.5) selama 15 minit (FRWBH) (iv) gabungan rawatan oral curcumin (50mg/kg berat badan) + *whole-body fever range hyperthermia* 39.0°C (± 0.5) selama 15 minit (CUR+FRWBH). Bergantung kepada rawatan, berat badan anak tikus dan saiz tumor diukur sepanjang 28 hari eksperimen dijalankan. Parameter kajian darah seperti hemoglobin (Hb), platlet (PLT), sel darah merah (RBC), sel darah putih (WBC), limfosit (LYM), neutrofil (NEUT), nisbah platlet-limfosit (PLR) dan nisbah neutrofil-limfosit (NLR) pada hujung eksperimen telah dikaji pada penghujung eksperimen (hari ke-28). Tempoh hayat median juga telah ditentukan untuk setiap kumpulan. Hasil kajian mendapati bahawa rawatan gabungan (FRWBH+CUR) merencat pertumbuhan tumor sebanyak 82.91% dengan perbezaan yang signifikan ($p=0.0440$) berbanding kumpulan kawalan. Anak tikus yang menerima rawatan FRWBH+CUR menunjukkan tempoh hayat median yang paling lama iaitu 42 hari. Rawatan FRWBH +CUR juga didapati diterima baik dan selamat kepada anak tikus dengan peratusan peningkatan berat badan yang signifikan ($p=0.001$) berbanding kumpulan kawalan sehingga 28 hari eksperimen. Walaupun terdapat kekerapan berlakunya komplikasi normal kanser seperti anemia dan trombositopenia pada kumpulan yang menerima rawatan gabungan FRWBH+CUR, hasil kajian PLR dan NLR menunjukkan bahawa rawatan FRWBH+CUR memberikan dapatan prognosis yang lebih baik berbanding rawatan secara

berasingan. Kesimpulannya, gabungan rawatan *whole-body fever range hyperthermia* dan kurkumin menunjukkan kesan antitumor yang baik terhadap anak tikus-teraruh kanser payudara dan rawatan ini adalah berpotensi sebagai rawatan alternatif untuk kanser payudara.

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CAM	-	Complementary and alternative medicines
BSE	-	Breast self-examination
NST	-	Invasive carcinoma of no special type
IDC	-	Invasive ductal carcinoma
ILC	-	Invasive lobular carcinoma
ADH	-	Atypical ductal hyperplasia
DCIS	-	Ductal carcinoma in situ
DIN	-	Ductal intraepithelial neoplasia
IDP	-	Intraductal papilloma
ER	-	Oestrogen
PR	-	Progesterone
HER-2	-	Human epidermal growth factor receptor 2
20-MC	-	20-methyl- cholanthrene
DLA	-	Dalton's lymphoma ascites
EAC	-	Ehrlich ascites carcinoma
CHO	-	Chinese hamster ovary
CUR		Curcumin
HT	-	Hyperthermia therapy
WBH	-	Whole-body hyperthermia
IR	-	Infrared
RF	-	Radiofrequency
MW	-	Microwave
EM	-	Electromagnet
FIR	-	UV Far IR
FRWBH	-	Fever range whole-body hyperthermia
wIRA	-	Water-filtered infrared-a
DNA	-	Deoxyribonucleic acid
mDTX	-	Docetaxel micelles
TNBC	-	Triple-negative breast cancer
CSC	-	Cancer stem-like cells

FBS	-	Fetal bovine serum
PBS	-	Phosphate buffered saline
DMSO	-	Dimethyl sulfoxide
CO2	-	Carbon dioxide
RT	-	Radiotherapy
CT	-	Chemotherapy
CBC	-	Complete blood count
RBC	-	Red blood cells
WBC	-	White blood cells
Hb	-	Hemoglobin
LYM	-	Lymphocyte
NEUT	-	Neutrophil
RFS	-	Recurrence-free survival
OS	-	Overall survival
NLR	-	Neutrophil to lymphocyte ratio
PLR	-	Platelet-to-lymphocyte ratio

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CHAPTER 1

INTRODUCTION

1.1 Problem Background

Based on latest Global Cancer Incidence, Mortality and Prevalence (GLOBOCAN) statistics, breast cancer is the universally diagnosed cancer and the top cause of cancer death among female globally with 2,088,849 (11.6%) new cases (Bray *et al.*, 2018). In Malaysia, breast cancer accounted for 32.1% of all cancer among females and the incidence trends were getting higher from 2007 to 2011 (Azizah *et al.*, 2016).

Breast cancer is a malignant tumour that derives from the cells of the lobules, which are the milk-producing glands, or the ducts, which are the passages that drain milk from the lobules to the nipple, but can also innervate into the fatty and fibrous connective tissues of the breast (Matsen and Neumayer, 2006). It is a complex and heterogeneous disease with multiple tumour entities associated with distinguishing histological patterns and diverse biological features and clinical appearances (Weigelt and Reis-filho, 2009).

Breast cancer typically produces no symptoms when the tumour is small. However, the most common physical sign is a painless lump, and other common signs and symptoms include breast pain, swelling, thickening, or redness of the skin at the breast, and other nipple abnormalities such as spontaneous discharge attrition or retraction (American Cancer Society, 2018).

The mortality rate of breast cancer depends on the size, invasiveness, lymph nodes involvement, and extensiveness to other body parts. The reduction in mortality rates of breast cancer is based on various factors. Despite genetics, controlling the risk factors is by having improved lifestyle and improving the breast cancer

diagnosis, namely by having early, frequent, and accurate diagnosis including self-breast examination and the most reliable technique of mammography. Another method to decrease the mortality rate of breast cancer is by improving the treatment of breast cancer (Boyle, 2005).

There are numerous treatments of breast cancer, such as surgery (mastectomy), radiotherapy, endocrine therapy, biologic therapy, hormone therapy, drugs or chemotherapy, thermotherapy, or a combination of these regimens (Carlson *et al.*, 2009). Surgery is a common approach to localised breast cancer. Adjuvant therapy is frequently followed after surgery to confirm the full recovery and minimise the risk of metastases. Cancer cells that may not be seen during surgery are exposed directly to a high level of radiation to kill the cancer cells through radiation (RT). However, soreness, peeling, itching, and redness of the skin at the treated area are some side effects of RT. The skin may become moist and weepy in the treated area (Nounou *et al.*, 2015).

Endocrine therapy (ET) is performed with the purpose of either balancing or blocking hormones. However, a patient's menopausal status mostly influences the treatment efficacy and side effect of the treatment (Dhankhar *et al.*, 2010). Chemotherapy (CT) is recommended in the majority of HER2-positive breast cancers, high-risk luminal tumours and TNBC. CT is usually administered intravenously to reduce tumour size and prevent metastasis. Various drugs have been discovered for the treatment of breast cancer, such as Taxotere, Adrucil, Herceptin, Tykerb, Avastin, Taxol and Adriamycin (Kalra and Edwards, 2012). However, each drug has its own limitation and possible adverse effects on the patient, such as diarrhoea, rash, mucosal inflammation and febrile neutropenia (Pisano *et al.*, 2005).

Thermotherapy (known as hyperthermia) has been used in oncology for centuries by utilising external heat transfer from the outer surface towards the inside (Bleehen, 1982). Hyperthermia (HT) is the procedure to raise the temperature of a part of the body or the whole body above normal temperature. It is conducted for a defined period of time at range between 40–48°C. The temperature is sustained at a treated site for one hour or more to generate the antitumour activity by heat.

Hyperthermia is conducted locally, regionally, or to the whole body. Hyperthermia is commonly used as an adjuvant and combined with other types of breast cancer treatments, such as radiotherapy, chemotherapy, surgery and immunotherapy (Vincze *et al.*, 2015).

Local hyperthermia can be conducted using external or internal devices. It is generally used for solid and localised diseases at or near the surface of the skin. Regional hyperthermia is used for diseases in deeper tissues or a larger area of treatment. Whole-body hyperthermia is normally used to treat tumours locally or whole body (globally) in metastatic disease (Mallory *et al.*, 2015). In whole-body hyperthermia, energy is introduced into the body and the loss of energy is minimised to elevate body temperature. It is normally conducted over a 6–12 hours duration with low temperature (39–42°C). It is well-established that cancer cells are killed and sensitised to chemotherapy or radiotherapy within this range (Joan M.C. Bull *et al.*, 2008).

Due to the severe side effects of cancer therapy and the elevated death rate related to cancer, many cancer patients seek alternative complementary and alternative medicines (CAM) as a method of treatment. CAM is valuable in cancer treatments by reducing the side effects and complications through conventional treatments (Mitha *et al.*, 2013a). CAM is comprised of natural herbal medicines and plants allegedly equipped with various biological and molecular mechanisms by inhibiting the growth of cancer (anticancer), thus protecting the body from malignancy.

Since early times, herbal plants are widely used in traditional medication. Some of the plants that have been actively studied for biological activities are Centella asiatica L., Curcuma Longa, Clinachantus nutans, Peperomia pellucida, Zingiber officinale, Polygonum minus, Boesenbergia rotunda, Azadirachta indica, Phyllanthus amarus, and Cymbopogan nardus. These plants have been reported to offer pharmacological and chemical properties, such as anti-inflammatory (Abdulla, Younis and Hassan, 2010, Chainani-wu, 1999), antiviral (Kim *et al.*, 2009),

antimicrobial (Onyeagba *et al.*, 2004), antioxidant (Huda-Faujan *et al.*, 2009) and anticancer properties (Kuttan *et al.*, 1985, Wei *et al.*, 2011).

The presence of various compounds in plants with anticancer effects renders them worthwhile to study. The compounds such as flavonoids (Ghasemzadeh *et al.*, 2010), catechins (Manikandan *et al.*, 2012), betulinic acid (Mullauer *et al.*, 2010), catechol (Nair *et al.*, 2009), alkaloids and tannin (Ismail *et al.*, 2000) and curcumin (Maheshwari *et al.*, 2006) have been studied and exhibited with anticancer effect.

Curcumin is one of the compounds in the herb plant Curcuma longa (turmeric). Turmeric is a native plant in South Asia and belongs to a rhizome plant of the family Zingiberaceae. Turmeric was scientifically studied and firstly reported with anticancer properties by (Kuttan *et al.*, 1985) with its relevant compound. Several in vitro and in vivo studies indicate that C. longa has antioxidant, anticancer, antitumour, antiviral, anti-diabetic, anti-inflammatory, and wound healing effects (Lin *et al.*, 2007, Kunnumakkara *et al.*, 2007, Aggarwal *et al.*, 2013, Maheshwari *et al.*, 2006, Chen *et al.*, 2016. Turmeric was reported to exhibit activity against the development of breast cancer by Deshpande, Ingle and Maru, 1998 and Bhide *et al.*, 1994.

Turmeric is a chemically diverse plant with approximately 235 compounds that have been identified, such as curcuminoids, turmerones, elemene, furanodiene, cyclocurcumin, calebine A and germacrone, diarylpentanoids, monoterpenes, sesquiterpenes, diterpenes, triterpenoids, alkaloid and sterols (Aggarwal *et al.*, 2013). Other newly identified constituents in this spice are cyclocurcumin, cyclodemethoxycur- cumin and cyclobisdemethoxycurcumin. However, there are still several unidentified constituents in turmeric with antitumour effects (Jiang *et al.*, 2012).

The major pharmacologically active ingredient of turmeric is curcuminoids. The most common antitumour constituents of curcuminoids are curcumin (diferuloylmethane), demethoxycurcumin and bisdemethoxycurcumin. Curcumin is the most widely studied constituent and a potent agent to prevent and treat cancer

(Aggarwal *et al.*, 2003). Its yellow-orange dye is derived from the plant C. longa. Various studies that combined curcumin with other breast cancer modalities such as CT (Bayet-Robert *et al.*, 2010; Yan *et al.*, 2013), and RT have been conducted and proven to have efficacy towards breast cancer. Scientific clinical trials of combination of curcumin with CT at phase I and II levels have entered 15 years of studies.

Hyperthermia is commonly combined with other types of breast cancer treatments, while a combination of curcumin with other breast cancer modalities is reported to have efficacy towards breast cancer. Thus, this study will provide the development of an alternative anticancer therapy of whole-body hyperthermia treatment with a combination of curcumin, which is a constituent of the herbal plant turmeric.

1.2 Problem Statement

Current common treatments in breast cancer are surgery, radiotherapy, chemotherapy and thermotherapy. At the moment, surgical is the option to remove solid tumours and patients receive adjuvant radiation treatment, chemotherapy and hyperthermia therapy. These treatments are usually in combination, such as surgery with chemotherapy, radiotherapy with chemotherapy, hyperthermia with radiotherapy.

Even though adjuvant systemic therapy is assisting in survival advantages for many women with breast cancer, toxicities are associated with this therapy (Rakha *et al.*, 2010). Chemotherapy has limitations and possible adverse effects on the patient, such as diarrhoea, rash, mucosal inflammation and febrile neutropenia (Pisano *et al.*, 2005). Due to the severe side effects of chemotherapy and the elevated death rate related to cancer, many cancer patients seek alternative complementary and alternative medicines (CAM) as a method of treatment.

CAM is valuable in cancer treatments by reducing the side effects and complications through conventional treatments (Mitha *et al.*, 2013a). CAM is comprised of natural herbal medicines and plants that are allegedly equipped with various biological and molecular mechanisms by inhibiting the growth of cancer (anticancer), thus protecting the body from malignancy.

Curcumin, a principal active ingredient derived from turmeric, has been proven to inhibit various breast cancer cells (Q. Zhou *et al.*, 2011; Masuelli *et al.*, 2013; Lv *et al.*, 2014) and breast cancer tumour growth (Farhangi *et al.*, 2015; Shiri *et al.*, 2015; Falah *et al.*, 2017). The anticancer effect of curcumin may also be seen when curcumin is combined with other treatment forms (Somers-Edgar *et al.*, 2008; Q. Zhou *et al.*, 2011; Falah *et al.*, 2017).

It has been reported that hyperthermia is cytotoxic to breast cancer cells (Lee *et al.*, 2014; Kossatz *et al.*, 2015). However, there is a probability that hyperthermia may not kill some of the cancer cells during the treatment and permits tumour growth regardless. The tumour microenvironment such as new vasculature may decrease the response of the tumour to heat and make the tumour grow (Baronzio *et al.*, 2014). The inability of homogenous heat distribution to the entire tumour and short response duration of the treatment (Behrouzkia *et al.*, 2016) have limited the effect of hyperthermia towards breast cancer. Besides, the exposure temperature and exposure time used are insufficient to damage all cancer cells. Thus, increased temperature, time of exposure and rate of heating can increase tumour killing and encourage better cell damage during hyperthermia treatment (Mallory *et al.*, 2015).

Table 1.1 showed summary of previous studies regarding to hyperthermia treatment (HT) and curcumin in breast cancer. Hyperthermia is commonly combined with chemotherapy. However, hyperthermia treatment is short-lasting and chemotherapy has a toxicity effect on the patients. Thus, this research is conducted to focus on curcumin, a constituent from a local herbal plant (turmeric) to improve hyperthermia treatment (using a device from Heckel Medizintechnic GmbH, Germany) as an alternative treatment of breast cancer.

Table 1.1 Previous studies of hyperthermia treatment and curcumin in breast cancer

	Type of breast cancer treatment	**References**
1.	Hyperthermia (HT) + Radiotherapy (RT)	(Jones *et al.*, 2005a; Mallory *et al.*, 2015; Maluta and Kolff, 2015; Datta *et al.*, 2016; Conn *et al.*, 2017)
2.	HT + Chemotherapy (CT)	(Robins, 1984; Wondergem *et al.*, 1991a; Toyota *et al.*, 1998; R. Rowe *et al.*, 2010; B, 2018)
3.	RT + CT +HT	(Beverly.A. *et al.*, 1988; Muthana *et al.*, 2010)
4.	HT +Surgery	(Behrouzkia *et al.*, 2016)
5.	HT + Immunotherapy	(Behrouzkia *et al.*, 2016)
6.	Curcumin (CUR) 50µg/kg and 200 µg/kg	(Bachmeier *et al.*, 2007; Lv *et al.*, 2014)
7.	CUR (45mg/kg)	(Lai *et al.*, 2012)
8.	2 mg CUR in 50µl of corn oil	(Masuelli *et al.*, 2013)
9.	CUR (50mg/kg)	(Falah *et al.*, 2017)
10.	CUR + CT	(H. Zhou *et al.*, 2011; Lai *et al.*, 2012)

1.3 Research Objectives

This study attempted to combine hyperthermia therapy with curcumin. The objectives of this research are as follows:

(a) To observe the general toxicity effect of the combination treatment of fever-range whole-body hyperthermia with curcumin.

(b) To identify the response of breast tumour after the combination treatment of fever-range whole-body hyperthermia with curcumin.

(c) To examine the haematological parameters after the combination treatment of fever-range whole-body hyperthermia with curcumin.

1.4 Research Scope

This study was focused on the effectiveness of the combination treatment of Fever-range Whole-body hyperthermia with curcumin in breast cancer with the following emphasis:

(a) The body weight to observe general toxicity effect of the combination treatment.

(b) The tumour volume to identify the response of breast tumour towards the combination treatment.

(c) The median survival rate to identify the response of breast tumour towards the combination treatment.

(d) The haematological parameters – haemoglobin (Hb), red blood cells (RBC), platelet (Plt), white blood cells (WBC), lymphocytes (LYM) and neutrophils (NEUT) to observe the progression and side effects of the combination treatment.

1.5 Significance of study

Optimistically, this study will be supportive of innovative treatment for breast cancer patients and may lead to the combination of more local herbal plants with hyperthermia treatment as an alternative treatment for breast cancer.

1.6 Hypothesis

This study was conducted with below hypothesis:

(a) There is a significant difference in body weight gained in the combination treatment group compared to the control group and single treatment group.

(b) There is a significant difference in tumour volume in the combination treatment group compared to the control group and single treatment group.

(c) There is a significant difference in median survival in the combination treatment group compared to the control group and the single treatment group.

(d) There is significant difference in haematological parameters haemoglobin (Hb), platelet (Plt), red blood cells (RBC), white blood cells (WBC), lymphocytes (LYM) and neutrophils (NEUT) in combination treatment group compared to control group and single treatment group.

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LIST OF PUBLICATIONS

Indexed Journal

1. **Saim, H.,** Irna, M., Salim, M. and Jemon, K. (2019) 'Antitumour Effect of Fever Range Whole-body hyperthermia with Curcumin in Breast Cancer-induced Mice', *International Journal of Recent Technology and Engineering (IJRTE)*, Volume-8(2S2), pp. 297–301. **(Indexed by Scopus)**