Original Article

The Effect of Curcumin on *Staphylococcus aureus* Resistant to Aminoglycosides Isolated from Burn and Wound Infections

Ola Abbas Khdhair[1,2], Yazi Abdullah Jassim[2]

[1]College of Pharmacy, University of Babylon, Babylon, Hillah, Iraq, [2]Department of Biology, College of Science, University Babylon, Babylon, Hillah, Iraq

Abstract

Background: Thermal injury destroys the skin, the natural barrier to the external environment. As a result the burned area is prone to infection and colonization of microorganisms. The most common pathogenic colonizing bacteria are *Staphylococcus aureus. Staphylococcus aureus* is both a human commensal bacterium, as it is carried by a significant amount of individuals, and a possible infectious pathogen. Other prevalent bacteria in burn wounds are *Acinetobacter baumannii* and *Klebsiella pneumonia*. All these pathogenic species of bacteria can contribute to the inflammatory immune responses induced by thermal injuries. **Objectives:** This study was carried out to study the effect of curcumin on *S. aureus* bacteria resistant to aminoglycosides isolated from wounds and burns of patients attending to the Imam Sadiq Hospital and Specialized Burn Center in Medical City of Baghdad and Kufa. **Materials and Methods:** A total of 230 burn wound swab samples were taken from hospitalized patients who presented invasive burn wound infection from both sex. All swabs were subjected to conventional cultural methods for microbial enumeration by using blood and manitol salt agar and performed by the Vitek 2 Advanced Expert System. The most predominant bacterial isolate was *S. aureus*, and the rate of resistance in this isolates was determined by disk diffusion method on Molar Hinton Agar. **Results:** Bacteriology results showed 63 *S. aureus* isolates from 230 clinical specimens obtained from patients with burn and wound infection. And their resistance to antibiotics was kanamycin 63.3%; tobramycin 75.1%; gentamicin and amikacin 47%; and streptomycin and neomycin 54%. Curcumin aqueous extract showed inhibitory effects for *S. aureus*. Curcumin extract was viability on some cell lines such as Michigan Cancer Foundation-7 and the human hepatic cell line (human normal liver cell [WRL]) with IC50 108.1 and 158, respectively. **Conclusions:** The curcumin extract was found to have an antimicrobial effect on *S. aureus* that can give resistance to aminoglycosides antibiotics. The cytotoxic effect of curcumin made using 3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide (MTT) was very little or non-existent and this encourages its use as an antibiotic in humans. It also had an effective and powerful biological role against cancer cell line.

Keywords: Aminoglycoside, curcumin, MCF-7, WRL

Introduction

One of the most significant and possibly dangerous complications that develop in the immediate aftermath of an accident is burn wound infections. Gram-positive bacteria, Gram-negative bacteria, and yeasts that originated from the host's normal flora (gastrointestinal flora, upper respiratory flora), as well as from the hospital environment, subsequently invade these wounds.[1]

Burn injuries are the localized tissue reaction to an energy transfer from a physical (mechanical, thermal, electrical, or radiation) or chemical source, with or without a systemic reaction.[2] Globally 75% of all deaths following thermal injuries are caused by infections in patients with burns covering more than 40% of their entire body surface area, making infections a significant cause of morbidity and mortality in hospitalized burn patients. Numerous factors, including the nature of the burn injury itself, the patient's immunocompromised state, age, the severity of the injury, and the depth of the burn, as well as microbial factors such as type and number of organisms, production of enzymes and toxins, colonization of the burn wound

Access this article online

Quick Response Code:

Website: https://journals.lww.com/mjby

DOI: 10.4103/MJBL.MJBL_348_23

Address for correspondence: Mrs. Ola Abbas Khdhair, Department of Biology, College of Science, University Babylon, Babylon, 51002 Hillah, Iraq.
E-mail: ola.mohammed9911@gmail.com

Submission: 23-Mar-2023 **Accepted:** 21-May-2023 **Published:** 23-Jan-2026

How to cite this article: Khdhair OA, Jassim YA. The effect of Curcumin on *Staphylococcus aureus* resistant to aminoglycosides isolated from burn and wound infections. Med J Babylon 2025;22:1009-15.

site, and systemic dissemination of the colonizing organisms, contribute to the higher rate of nosocomial infections in burn patients.[3]

Although there is a high burden of burn injuries in the developing countries including Iraq, accurate and sufficient data about the epidemiological information of burns in these countries are limited and scattered. Burns form the fourth most common cause of injury after road traffic injuries, falls, and interpersonal conflicts.[4] More cases of resistance to aminoglycosides are been documented in clinical and microbiological contexts.[5] The inactivation of antibiotics by aminoglycoside-modifying enzymes (AMEs), which are encoded by genetic elements, is the primary route of resistance to aminoglycosides.[6] The most frequent AMEs in *Staphylococci*, according to clinical studies, are ANT (4')-I, AAC (6')/APH(2'"), and APH (3")-III, which modify aminoglycosides of therapeutic value, such as tobramycin, gentamicin, and kanamycin, respectively.[7]

Plants have long been used as a source of medicinal compounds. The antibacterial, antifungal, and anticancer effects of several plants have been the subject of numerous investigations. Herbal medications have long been utilized in dentistry as anti-inflammatory analgesic and antibacterial agents.[8] The medicinal plant turmeric, or *Curcuma longa* L., is a member of the Zingiberaceae family. It is a perennial plant that grows to a height of about three feet. The majority of rhizomes are oblong, pyriform, ovate, and frequently short-branched.[9] Numerous studies have proven curcumin's antibacterial action, showing it to have broad-spectrum bacterial inhibitory characteristics. This research's goals included identifying and isolating bacteria from burn sites and examining how curcumin affected the bacteria isolates. The quantity of healthy cells in a sample is a common way to define cell viability. Methods for determining cell viability can be divided into those that examine a population as a whole and those that focus on a single cell.[10]

Some anticancer medications trigger apoptosis by altering the permeability of the mitochondrial membrane, which results in the loss of mitochondrial membrane potential, a reduction in Bcl-2 levels, the release of cytochrome C, the activation of caspase-3, and the production of reactive oxygen species.[11] The pleural effusion of a 69-year-old woman who had breast cancer was used to make Michigan Cancer Foundation-7 (MCF-7).[12] The cell line has an epithelial-like morphology, and fluid collection between the culture dish and the cell monolayer causes monolayers to form dome formations. The estrogen receptor (ER) is only expressed by a small percentage of breast tumors.[13] Because of the presence of the ER, MCF-7 is incredibly sensitive to hormones, making it a preferred model to research hormone response.[14]

Materials and Methods

Sample collection and bacterial isolates

Study population included 230 participants with burn wound infection admitted burn unit in Imam Sadiq Hospital, Specialized Burn Center in Medical City of Baghdad and Kufa from February to July 2022. Burn wound swabs were taken from all patients registered in the study and immersed in Stuart's transport medium. From theses 230 only 63 burn wound swabs were *Staphylococcus aureus*. Swabs were collected from infected wound following cleansing of any remnant ointment. After collection, all swabs were inoculated on Blood agar, Mac-Conkey's agar and Manitol salt agar and incubated at 37ºC for 24 h. Morphological examination of these swaps and colonial morphology, production of β hemolysis on blood agar and production of pigmentation on Manitol salt agar revealed 63 isolates of *Staphylococcus* that were confirmed to be *S. aureus* by coagulase Manitol fermentation and ultimately confirmed by the Vitek 2 Advanced Expert System (bioMerieux, Marcy l'Etoile, France).

Drug susceptibility testing

Drug susceptibility testing was performed by disk diffusion method according to CLSI guidelines.[15] The standard bacterial suspension of *S. aureus* with turbidity equal to 0.5 McFarland was inoculated on Mueller Hinton agar (Merck, Darmstadt, Germany), using the following aminoglycoside antibiotics: gentamicin (10 mg), amikacin (10 mg), kanamycin (30 mg), tobramycin (10 mg), streptomycin (25 mg), and neomycin (30 mg) (Bioanalyase, Turkey). The plates were incubated at 37ºC for 24 h and the diameter of zone of growth inhibition was measured and compared with standard values.

Preparation of plant extracts

In this study *C. longa* (turmeric) was collected from commercial sources in Babylon, Iraq. Different concentrations of the turmeric curcuminoids were prepared in distilled water by using serial dilution method. The test organisms were seeded into respective medium by gently mixing 0.1 mL of the 24 h fresh cultures with 35 mL sterile melted agar in sterile petri plates. Four 7 mm diameter wells were made using sterile borer. The wells were filled with 0.1 µL of the sample extract. The antibacterial assay plates were incubated at 37ºC for 24 h. The diameter of the zones of inhibition around each of the well was taken as measure of the antibacterial activity. Each experiment was carried out in four dilutions (200, 100, 50, and 25 mL) of distilled water and mean diameter of the inhibition zone was recorded.

Table 1: Distribution of *Staphylococcus aureus* isolation

Sample sources	Sample collection locations			
	Hilla Teaching Hospital	Imam Sadiq Hospital	Specialized Burn Center, Najaf	Specialized Burn Center, Medical City, Baghdad
Burns No = 50	–	10	26	14
Wounds No = 13	13	–	–	–

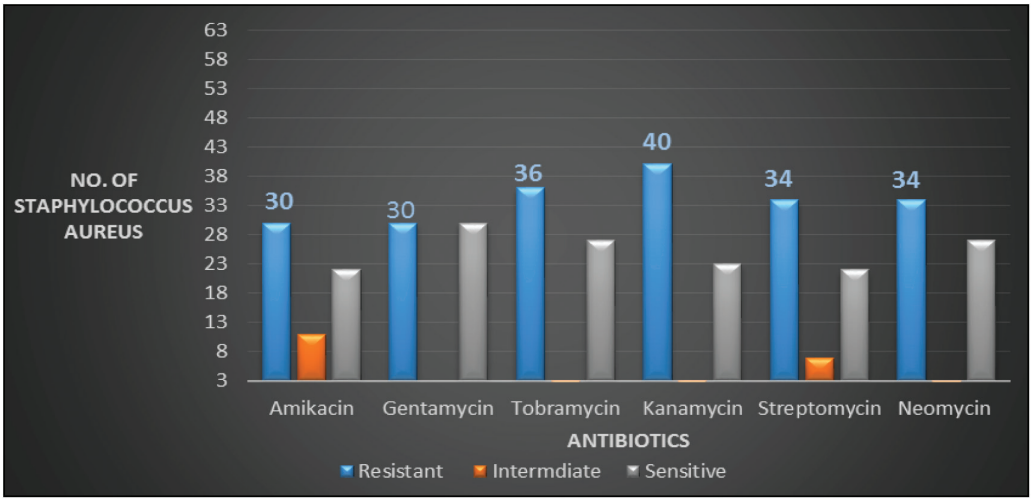

Figure 1: Susceptibility test of *Staphylococcus aureus* isolates to aminoglycoside antibiotics

Cell lines

MCF-7 cell line

The breast cancer pleural effusion of a 69-year-old woman was the source of MCF-7.[16] From the Center of Biotechnological Research in Malaysia, this cell line was obtained.

WRL 68 cell line

The morphology of the human hepatic cell line (human normal liver cell [WRL]) 68 is comparable to that of primary cultures and hepatocytes. According to research by Asita and Salehhuddin,[17] cells have been found to express liver-specific enzymes including alanine amino transferase and secrete albumin and alpha-feto protein.

Solutions and media used in tissue culture technique

Solutions and media used for cell culture were prepared according to Freshney.[18]

Media

Roswell Park Memorial Institute—1640 medium (RPMI)

A ready-to-use package (100 mL) RPMI was used throughout this study. The medium was already supplied with 4-(2-hydroxyethyl)-1piperazine-ethane sulfonic acid (HEPES) and L-glutamine as illustrated by manufacturer.

Serum free medium

Serum free medium is RPMI-1460 excluded from fetal calf serum.

Ethical approval

The study was conducted in accordance with the ethical principles that have their origin in the Declaration of Helsinki. It was carried out with patients verbal and analytical approval before sample was taken. The study protocol and the subject information and consent form were reviewed and approved by a local ethics committee according to the document number M220109 in January 17, 2022 to get this approval.

Results

Bacterial isolates

Out of 230 samples of burn and wounds patients, only 63 isolates were *S. aureus*. These isolates are distributed according to sample collection location as in Table 1.

Of the *Staphylococcus* isolates, 63.4% (40/63) were resistant to kanamycin, 57.1% (36/63) to tobramycin, 54% (34/63) to streptomycin and neomycin, whereas 47.6%

were resistant to (30/63) to gentamicin and Amikacin as shown in Figure 1.

The efficiency test of the aqueous curcumin extract was conducted with different concentrations (200, 100, 50, 25 mg/mL) on samples that were resistant to aminoglycosides. There was a clear inhibition for most samples, as the highest inhibition was for the higher concentration, and in some samples, all concentrations gave clear inhibition with different diameters in Figure 2.

Effect of curcumin extract on MCF-7 cell lines viability

Curcumin extract as in Table 2 inhibits the cellular growth for human breast cancer MCF-7 cell lines. The viability of MCF-7 cell line was 4.82%, 4.28%, 9.30%, 30.67%, 54.47%, and 62.38% in 12.5, 25, 50, 100, 200, and 400 µg/mL, respectively, from curcumin extract.

Effect of curcumin extract on WRL cell lines viability

Curcumin extract in Table 3 and Figure 3 inhibits the cellular growth for WRL cell lines. The viability of WRL cell line was 4.1%, 4.8%, 4.7%, 7.6%, and 17.3% and 22.3 in 12.5, 25, 50, 100, 200, and 400 µg/mL, respectively, from curcumin extract with IC50 158.

Discussion

In patients with thermal injuries, bacterial infections of the burn wound continue to be a major source of morbidity and mortality. The patient who has been burned is vulnerable to a wide range of germs because the wound has a huge surface area, a lot of dead tissue, and free serum exudate that is ideal for bacterial development. The burn site initially develops a colony of bacteria that, if left unchecked, progress to invasion and result in bacteremia

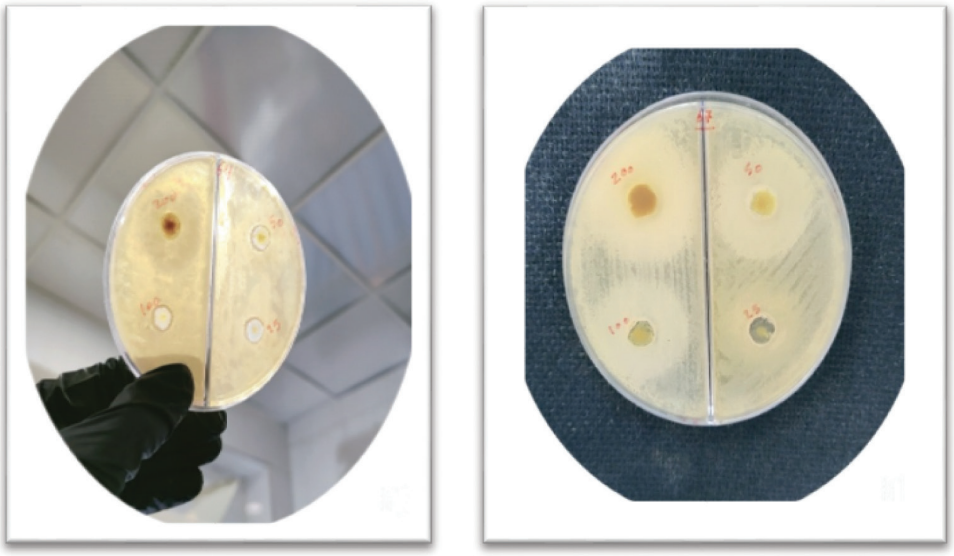

Figure 2: (a) Inhibition zone of *S. aureus* with curcumin aqueous extract with all concentration. (b) Inhibition zone of *S. aureus* with curcumin aqueous extract only with 200 mL concentration

Table 2: The effect of curcumin extract on the viability of MCF-7 cell lines

MCF-7	Cell viability %						IC50
	Concentration of extract curcumin (M ± SD)*						
	400 µg/ml	200 µg/ml	100 µg/ml	50 µg/ml	25 µg/ml	12.5 µg/ml	
Curcumin	37.62 ± 3.451	45.53 ± 4.245	69.33 ± 3.151	90.70 ± 3.183	95.72 ± 3.183	95.18 ± 1.280	108.1
Dimethyl sulfoxide DMSO	87.95 ± 6.288	92.52 ± 1.603	94.33 ± 1.917	92.70 ± 1.708	95.72 ± 0.8102	95.18 ± 1.280	

* M: mean, SD: standard deviation

Table 3: The effect of curcumin extract on the viability of WRL cell lines

WRL	Cell viability %						IC50
	Concentration of extract curcumin (mean ± SD)						
	400 µg/mL	200 µg/mL	100 µg/mL	50 µg/mL	25 µg/mL	12.5 µg/mL	
Curcumin	77.74 ± 3.21	82.75 ± 2.84	92.44 ± 2.71	95.33 ± 1.18	95.22 ± 0.820	95.95 ± 1.02	158
Dimethyl sulfoxide DMSO	92.41 ± 1.88	94.42 ± 0.886	92.44 ± 2.71	95.33 ± 1.18	95.22 ± 0.821	95.95 ± 1.02	

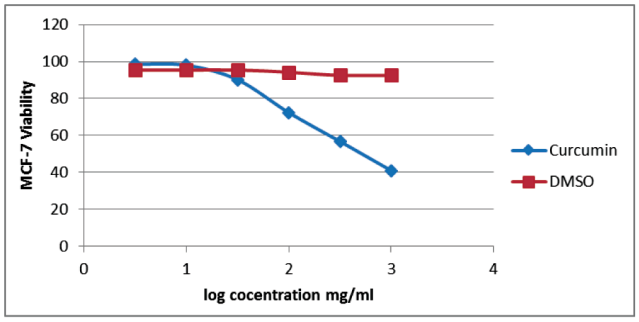

Figure 3: Effect of curcumin extract on Michigan Cancer Foundation-7 cell lines viability

and sepsis, which are key factors in burn patients' mortality. Although burn wound infections can be diagnosed clinically, more microbiological proof is required for the implementation of effective therapy.[19] The swabs that were sent for culture in our investigation tested positive for *S. aureus*. In the days before antibiotics, *Staphylococcus* was the leading cause of burn wound infection and it is still a significant pathogen today. However, according to Srinivasan *et al.*,[20] *staphylococci* % incidence decreased from 2002 to 2005. Antibiotic sensitivity patterns provided a helpful framework for selecting the best antibiotic. We found that bacterial isolates in our investigation were have resistance to aminoglycoside antibiotics (Kanamycin, Tobramycin, Streptomycin, Neomycin, Gentamicin, and Amikacin) respectively. Although aminoglycosides continue to be active against the majority of Gram-positive clinical bacterial isolates in many regions of the world, doctors are hesitant to use these drugs in routine practice because to the relatively common occurrence of nephrotoxicity and ototoxicity during treatment.[21] Physicians should reevaluate these "old" antibacterial drugs, though, in light of the recent rise of diseases caused by Gram-negative bacteria with advanced patterns of antimicrobial resistance.[22] However, localized use of aminoglycosides may quickly cause *staphylococci* to develop antibiotic resistance, reducing the effectiveness of prophylaxis.[23] From one nation to another and from one year to the next, *staphylococcal* resistance to aminoglycosides varies.[24] Schmitz *et al.*[25] reported in a 1999 European multicenter study that 23%, 29%, and 31% of *S. aureus* were resistant to gentamicin, tobramycin, and kanamycin, whereas Hope *et al.*[24] reported that 9% of MRSA and 2.5% of MSSA were resistant to gentamicin, collected from bacteremia cases in the UK and Ireland between 2001 and 2006. The swabs that were sent for culture in our investigation tested positive for *S. aureus*. In the days before antibiotics, *Staphylococcus* was the leading cause of burn wound infection and it is still a significant pathogen today. However, according to Srinivasan *et al.*, *staphylococci* % incidence decreased from 2002 to 2005. The current study's overall incidence of aminoglycoside resistance was higher than the incidence seen in other publications from Iran. For instance, in a recent study in Iran (2019), 102 clinical isolates of *S. aureus* had resistance percentages of 83% to kanamycin, 76% to tobramycin, 71% to gentamicin, and 59.5% to amikacin.[26]

In a subsequent investigation conducted in Iran in 2009, 100 clinical isolates of *S. aureus* were shown to be 68% resistant to kanamycin, 53% resistant to tobramycin, 52% resistant to gentamicin, and 48% resistant to amikacin.[27] Selecting bacteria with a known resistance trait rather than randomly chosen isolates may be the cause of this discrepancy. Only a few *S. aureus* isolates in the current investigation were pane-resistant, whereas the majority of *S. aureus* isolates were multi-drug resistant. Continuous use of broad-spectrum antibiotics and disregard for a hospital's antibiotic policy may be to blame for this. Additionally, the most likely cause of the elevated resistance in patient isolates could be attributed to the selection pressure in the hospital wards.[27]

The availability of therapeutic alternatives for the effective treatment of burn wound infections is constrained by the evolution of global antimicrobial resistance among a number of human, bacterial, and fungal burn wound pathogens, particularly nosocomial isolates.[28] Turmeric is a well-known indigenous herb with numerous biological effects.[29] Some of the *S. aureus* strains showed significant inhibitory activities. The results are similar to other studies.[30] An notable finding of our investigation is the apparent shift in the gram-positive cocci from the usually significant gram-negative rods in burn wound microbiology. *S. aureus* in burn patients may have an external source. The high level of *S. aureus*, especially MRSA, contamination of the environment's surfaces and air supports this conclusion. It is evident that control measures should be focused on preventing *S. aureus* contamination of the environment given the significant amount of contamination of the air and bath carts that was observed. The causes of prevalence could be complicated illnesses, preceding treatment of antimicrobial drugs, the immunosuppressive effects of burn injury, or factors related to nosocomial pathogen acquisition in patients with recurrent or long-term hospitalization An extensive spectrum of pharmacological effects are known to exist in the main component of the spice turmeric (*C. longa* L.), which is frequently used in Asian cuisine, at relatively low dosages.[31] For many years, turmeric has been used for medical purposes in India. It is one of nature's most powerful healers. Turmeric is an ancient spice made from the rhizomes of *C. longa*, a member of the ginger family (Zingiberaceae).[32] Curcumin provides turmeric its yellow hue and is now recognized for having the majority of medicinal benefits; it makes up an estimated 2%–5% of turmeric.[33] It fights cancer during the beginning, promotion, and progression stages of tumor formation because it contains a combination of potent antioxidant phytonutrients called curcuminoids. It is a

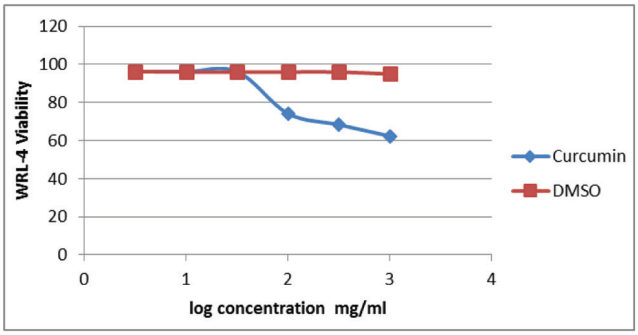

Figure 4: Effect of curcumin extract on human normal liver cell (WRL-4) cell lines viability

potent antioxidant that supports intestinal health, has neuroprotective effects, and promotes cardiovascular system health.[34] In the current study, it was found that the aqueous extract of curcumin has the effectiveness of inhibiting the growth of burn wound bacterial isolates at different concentrations, as it was the strongest inhibition of the extract when the concentration was 200 mg/mL of distilled water. According to reports, plant extracts can more easily kill Gram positive bacteria.[35] Among gram positive bacteria, *staphylococcus aureus*, Alzoreky and Nakahara[36] conducted a study. The healing of wounds is facilitated by a variety of natural chemicals, plant compounds made of active components such triterpenes, alkaloids, flavonoids, and biomolecules.[37] Curcumin has antibacterial and antioxidant properties, and additionally, it can hasten the re-epithelialization of cells needed for wound healing, including macrophages, fibroblasts, and myofibroblasts.[38] Combination antibiotic therapy is increasingly utilized to reduce the possibility of bacterial resistance to antibiotics and to broaden the antibacterial spectrum during the course of treatment.[39] Several studies have demonstrated that mixing antibiotics with unrefined plant extracts can increase the effectiveness of their antibacterial effects.[40]

The results of cytotoxic effect of curcumin adverted that treating MCF-7 cells at concentrations ranging from 12.5 to 400 µg/mL for 24 h showed a significant mortality in cell viability by increasing the concentration in a dose dependent pattern that reached up to 62% killing at 400 µg/mL with an half inhibition concentration (IC_{50}) of 108.1 µg/mL [Figure 3, Table 2]. Numerous studies have shown the effectiveness of curcumin and its use as an anti-cancer that fights the growth of cancer cells, including research of Shen *et al.*[41] revealed the therapeutic potential of the curcumin analog B14 and the underlying mechanisms to fight breast cancer cells. In contrast, the treatment of WRL cells with curcumin appeared to be less affected by applying the same concentration range with a detected IC_{50} of 158 µg/mL [Figure 4, Table 3]. In the two cases, when using the compound DMSO at concentrations ranged (400–12.5 µg/mL), found that there was no significant effect on the viability of the cell lines (MCF-7 and WRL).

Financial support and sponsorship
Nil.

Conflicts of interest
There are no conflicts of interest.

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