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Review Article

Antimicrobial Activity and Medicinal Plants in the North and East of Syria: A Review Study

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Abstract
Herbal plants contain a medicinal source with antimicrobial properties that offer a safer and more cost-effective method to treat human pathogens. Scientists in the field are performing research on plants to discover their potential antimicrobial compounds. This study aimed to conduct a review of the antimicrobial and antioxidant properties and investigate particular herbal plants with medicinal activities in the north and east of Syria. Considering that some herbal plants, including *Cuminum cyminum*, *Mentha piperita*, *Allium cepa*, *Majorana hortensis*, *Eucalyptus camaldulensis*, *Thymus capitatus*, *Achillea millefolium*, *Malva parviflor*, and *Capparis spinose*, have antifungal, antimicrobial, and antioxidant activities, the products obtained from these plants may be used to control the growth of pathogenic microorganisms. In addition, this study focused on the chemical compounds, including p-cymene, kaempferol, quercetin, capsaicin, 1,8-cineole, flavonoids, gallic acid, and alkaloids, which play a role in inhibiting microbial growth. Based on the results obtained from this review study, using these herbal plants can control human infectious, pathogenic, cancerous, and antioxidant diseases.
Keywords: Herbal plant, Antimicrobial activity, Antibiotic, Infectious pathogens

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Introduction
Pathogenic microorganisms have been one of the most serious threats to human beings since their inception and are the main cause of human mortality. The world's population mainly depends on traditional medicine, which consists of herbal plant extracts or their active ingredients and is a cheap and reliable alternative to chemical drugs (1). Herbal plants in traditional medicine are one of the main sources for the treatment and prevention of a wide number of diseases and are used as therapeutic agents to improve health (2). It has been estimated that traditional medicine provides for and supports about 80% of health needs (3). To overcome the downside of drug resistance, obtaining new molecules from natural resources such as plants deems necessary (4). Plants contain secondary metabolites, including phenols, alkaloids, saponins, terpenes, lipids, and carbohydrates (5). Antimicrobials, including antivirals, antifungals, and antibacterials, are mostly utilized to treat pathogens in humans (6). Chemotherapy with antimicrobials has made great progress recently; accordingly, infectious diseases might prevail in the future. However, infections with drug-resistant organisms are considered a major issue in clinical practice (7).

The cytotoxic and antimicrobial activities of herbal plants found in Syria have been reported during the past decades (8). Jaradat et al tested the cytotoxic properties of 61 herbal plants and found some compounds, including oleander and oleuropein (9). Oleuropein, a phenolic compound, inhibits reproduction by inducing apoptosis in breast cancer cells, such as MCF7 cells, and suppresses cell cycle development in the G1 phase (10).

Syria is known for its herbal plants with medicinal and antimicrobial properties that have been used since ancient times. Traditional medicine is one of the important medical systems in Syria, where people use different natural substances as medicinal sources (11). In this country, there are a large number of vascular plants (approximately 3500) belonging to 131 genera. Palmyra is an ancient city in Syria and the richest region with herbal plants. In the north and east of Syria, herbaceous plants, including *Allium cepa*, *Allium sativum*, *Citrullus colocynthis*, *Coriandrum sativum*, *Teucrium polium*, *Foeniculum vulgare*, *Olea europaea*, *Sarcopoterium spinosum*, *Matricaria aurea*, and *Foeniculum vulgare*, are employed to treat diabetes, heart diseases, liver diseases, infectious pathogens, and cancer (12,13).

Based on the reports on the resistance of human pathogenic microorganisms to synthetic drugs, it seems necessary to identify medicinal plants and their chemical compounds in order to prevent and control diseases, especially infectious diseases. The review sought to investigate the antimicrobial and antiradical properties of plants. It also evaluated some herbal plants in the north and east of Syria that can be used to treat and control pathogenic microorganisms.

Herbal Plants

Egyptians and Chinese seem to have been the first humans to utilize plants as medicine over 27 centuries BC and even used some plants for pain relief. Natural products derived from herbal plants are the main source of pharmaceutical preparation and the primary basis for the development and improvement of medicinal compounds (14,15). Bacterial resistance to combinations of drugs, such as herbal extracts, is slower than to drugs made from a single compound (16,17). There are about 500 000 plant species in the world, only 1% of which have been studied for medicinal purposes (18). Resistance to antibiotics by infectious microbial agents has encouraged researchers to screen for herbal plants with antimicrobial activities (19). Therefore, herbal plants are a very good potential source for the discovery of new drug compounds (20).

Antibacterial Plants

The bacteria that cause diseases and infections are called pathogenic bacteria, and researchers have developed antibacterial agents as broad-spectrum chemotherapy (21). Outer member (OM), which is a lipid bilayer containing phospholipids, is found in Gram-negative bacteria; however, Gram-positive bacteria lack this membrane. In addition, the outer leaflet of the OM is composed of lipopolysaccharides (22), and some proteins, including lipoproteins and beta proteins, are present in the OM. OMs act as the front line of defense against bile salts and antibiotics, which are responsible for the low permeability of lipophilic cells (23). Cell wall peptidoglycan, as the second layer, is a tough outer structure that defines the shape of the cell and is also composed of the repeating unit of the polysaccharide N-acetyl glucosamine-N-acetylmuramic acid (24). The inner membrane is a phospholipid bilayer responsible for multi-purpose processes, such as structural transduction and biosynthetic functions, and is the third layer (25).

The teichoic acids are present in the cell walls of Gram-positive bacteria, which contain lipoteichoic acid covalently anchored to peptidoglycan by glycolipid (26). Further, porins in Gram-negative bacteria are peptidoglycan-associated proteins, which are important because hydrophilic nutrients should pass through them in the OM (27).

Resistance Mechanisms of Pathogens

Target Modification

The target modification of the endogenous resistance mechanism against a wide range of antibiotics, including streptogramins, macrolides, β-lactams, glycopeptides, lincosamides, and aminoglycosides, is taken into consideration (28). Deactivation of antibiotics in bacteria is observed in enzymatic changes through the addition of bacterial enzymes acetyl phosphate to a specific site of antibiotics to chemically modify them and deactivate the antimicrobial agent (29). The direct binding between bacterial enzymes and antibiotics by the hydrolysis of antibiotics, such as beta-lactamase against penicillin and cephalosporins, causes the occurrence of the enzymatic inhibition process (30).

Efflux Pumps

Efflux pumps are the main mechanism in antibiotic resistance in Gram-positive and Gram-negative bacteria (31). These pumps have emergency resistance, thus allowing bacteria to develop mechanisms to defend themselves when suddenly exposed to antibiotics or toxic agents. Bacteria contain five families of efflux pumps (32). The substrate of the *Escherichia coli* housekeeping efflux system is AcrAB-TolC (33). The AcrAB-TolC efflux system in *Salmonella typhimurium* can destroy antimicrobial agents, including tetracyclines, quinolones, chloramphenicol, and nalidixic acid (34). *Pseudomonas aeruginosa* are two Resistance-nodulation-division (RND) efflux pumps that constitutively express MexAB–OprM and can export fluoroquinolones, tetracycline, and chloramphenicol (35).

β-Lactamases

β-Lactam antibiotics bind to penicillin-binding proteins (PBPs), which are cell wall synthesis enzymes, and inhibit peptidoglycan synthesis (36). Deterrence of PBPs results in the weakening of the cell wall, leading to growth inhibition or cell death. Reduced accessibility to PBPs, reduced PBP binding affinity, and degradation of an antibiotic through β-lactamase expression are the mechanisms of β-lactam resistance (37). In gram-positive bacteria where PBPs are present, antibiotics quickly reach the cytoplasmic membrane of bacteria. Moreover, the OM of the gram-negative bacteria can limit the entry of beta-lactams and increase beta-lactamase molecules (38).

Antioxidants

Antioxidants are a group of chemicals that have the ability to prevent or reduce oxidative stress in the physiological system. It is known that the body constantly produces free radicals, which are responsible for the damage to body cells. Plants are the most important natural sources of antioxidants, which are classified into water-soluble and fat-soluble categories (39). Vitamins C and E are the most important water-soluble and fat-soluble antioxidants, respectively (40).

Maintaining coordination between antioxidants and free radicals is an essential factor for staying healthy. Therefore, controlling oxidative stress activity plays an essential role in the inhibition and treatment of a large range of diseases, including diabetes, apoptosis, infections, nephrotoxicity, liver disease, and cardiovascular disease (41).

The activity of antioxidant compounds is typically performed by reducing the activity of free radicals, eliminating free radicals, combining with oxide precursors and reactive oxygen atoms, and removing catalytic metal ions, such as Cu^{2+} and Fe^{2+} (42).

Plant Antioxidants

In recent years, a wide range of research has been conducted to investigate the potential of plant products as antioxidant compounds against diseases. Most secondary metabolites with medicinal properties have antioxidant activities by inactivating free radicals and reactivating oxygen species produced by aerobic metabolites (43). Most chemical compounds found in plants, including flavonoids, fibers, phenolic compounds, and isoflavones, have antioxidant properties through the destruction of free radicals (44). Phenolic compounds protect cellular chemical compositions from oxidative harm, thereby limiting the risk of different diseases that lead to oxidative stress. Experimental studies have shown that phenolic and flavonoid compounds can play a role in inhibiting some diseases, including cancer, apoptosis, osteoporosis, and neurological diseases (45). Flavonoids can have a vital anticancer role by inhibiting the polymerization of tubulin and preventing the destructive action of free radicals (46).

Today, artificial antioxidants, including butylated hydroxy anisole, tertiary butylhydroquinone, and butylated hydroxytoluene, are used to delay the oxidation of lipids. The acceptability of natural additives and the harmful and toxic effects of synthetic antioxidants have increased the tendency to use natural antioxidants (47).

Free Radicals

Free radicals contain an unpaired, highly reactive electron, which can donate and accept this electron from other molecules, and thus act as an oxidizing or reducing agent. Free radicals, along with reactive nitrogen species (RNS) and reactive oxygen species (ROS), play a dual role in the biological system, which is of significant importance in terms of the signaling network in plants. ROS and RNS produced in oxygen metabolism are important in regulating gene expression, cell proliferation, apoptosis, protein phosphorylation and activation in cells, and microorganism elimination (48).

In a normal cell, there is an antioxidant balance, and when the production of radicals is excessive, the body's defense mechanisms fail and cause the destruction of biological molecules, including DNA and protein (49).

Due to the action of antioxidants, there are two main mechanisms, one for the chain-breaking mechanism by the initial antioxidant, which awards an electron to free radicals, and the other for the removal of pathogens by the quenching of RNSs (50).

Antifungal

In general, fungi are unicellular or multicellular eukaryotic organisms that are found in all environments of the world (51). An antifungal drug is a factor that selectively kills fungal pathogens from the host with the least toxicity. Fungi have eukaryotic functions for cells, making them more closely related to humans than to bacteria (52). However, according to scientific reports on more than 2 million fungal species, 600 fungal species are known to be pathogenic to humans, and only 3–4% of these species score for more than 99% of the invasion of fungal infections (53).

Candida species, including *Candida parapsilosis*, *C. albicans*, *C. krusei*, *C. glabrata*, and *C. tropicalis*, have emerged as invasive candidiasis, with a mortality rate of up to 75% as it generally affects the respiratory and digestive systems and skin (54). During the 1950s, more than 200 polyenes with antifungal activities were obtained; however, amphotericin B remains the most popular polyene drug for the treatment of fungal pathogens (55). Caspofungin, micafungin, and anidulafungin are the newest and best classes of peptide antifungals (56). *Aspergillus fumigatus* is responsible for 90% of the invasion of aspergillosis and causes relentless pneumonia. *Basidiobolus ranarum* mainly causes subcutaneous disease in children (57), and an endemic disease called Sporotrichosis is caused by the dimorphic fungus *Sporothrix schenckii* (58).

Some antifungal agents, including azoles and imidazoles, can noticeably prevent 14a-demethylation in the biosynthesis of ergosterol. The main molecular target of azole antifungals is called cytochrome P450-Erg11p or Cyp51p. Azole resistance can be caused by the activation of membrane pumps that release antifungals from the cell or mutations that alter the target azole molecule (59).

Polyenes belong to the amphipathic class of nature and form pores that allow small molecules to pass through the membrane and lead to cell death (60). According to recent reports, amphotericin B and nystatin are the two main polyenes, and amphotericin B is called the gold standard in the treatment of major fungal infections, including *Candida*, *Cryptococcus*, and *Aspergillus* (61).

Antibiotics

The term antibiotic is derived from anti-biosis, which means anti-vital, and is classified into synthetic or semi-synthetic. The discovery of antibiotics has been one of successful discoveries throughout human history. Antibiotics are a class of drugs that are used to treat bacterial infections but are not effective against other viral infections (62). Alexander Fleming was the first to discover penicillin in the late 1920s. Penicillin successfully controlled bacterial infections among World War II soldiers. The most important antibiotics included penicillins, cephalosporins, tetracyclines, aminoglycosides, chloramphenicol, macrolides, and glycopeptides (63).

Natural antibiotics are antimicrobial compounds that are produced by bacteria and fungi and are used as therapeutic agents. They might also be utilized to prevent and control infectious diseases. These compounds are a large group of substances that cause bacteriostatic or bactericide effects. In developed countries, the spread of infectious diseases is still a serious problem (64). Today, because of the improvement of drug resistance, the high cost of treatment with synthetic drugs, and the observation of the side effects of some antibiotics, researchers have discovered antibacterial compounds in herbal plants (65).

Antibiotic Mechanisms

Inhibition of Membrane Function

The bacterial membrane is often the target of antimicrobial peptides. The OM in Gram-negative bacteria is rich in lipopolysaccharides and antimicrobial peptides that prevent the passage of solutes between the surrounding layer and the outer part of the cell and cause bacterial toxicity. The main component of bacterial lipids, such as phosphatidylglycerol, in Gram-positive bacteria can be chemically changed through bacterial enzymes to convert lipids from an anionic to cationic form, which increases the level of bacterial resistance against multivalent antimicrobial agents (66,67).

Daptomycin is a group of antibiotics that is a lipid antagonist and has a new mode of action. In addition, it is composed of 13 amino acid cyclic lipopeptides with a hydrophilic core and a lipophilic tail. The activity of daptomycin is membrane depolarization and demonstrates the relationship between membrane depolarization and bactericidal properties. The fatty tail of daptomycin is inserted into the membrane of the cell wall in a calcium-dependent manner and forms a K channel for extracellular transport by the contraction of daptomycin molecules (68).

Telavancin changes the permeability of the cell membrane and disperses the potential of the membrane. However, telavancin is 10 times more active than vancomycin in inhibiting glycosylation and binding peptidoglycan (69).

According to recent reports, broad-spectrum antibiotics, such as fosfomycin, inhibit phosphoenol pyruvate transferase, which is involved in the synthesis of peptidoglycans in some bacteria, including *Staphylococcus aureus*, penicillin-resistant, *Enterococcus pneumoniae*, *E. coli*, and *Klebsiella pneumonia* (70).

Inhibition of Protein Synthesis

The ribosome organelle consists of two ribonucleoprotein subunits, including 50S and 30S (71), and the drugs that prevent the synthesis of protein can be classified into 50S and 30S inhibitors. Some inhibitors, including lincosamide, macrolide, amphenicol, streptogramin, and oxazolidinone, can be used for ribosome 50s inhibitors. Moreover, tetracycline and aminocyclitol inhibitors can be utilized for the 30s ribosome (72).

Inhibition of Nucleic Acid Synthesis

The prevention of nucleic acid synthesis can be divided into RNA and DNA inhibitors. Metronidazole diffuses into the organism and prevents protein synthesis by interacting with DNA, causing the destruction of the helical structure of DNA and strand breakage, and cell death in organisms (73). RNA inhibitors, the first specific inhibitory effect of rifampin on the RNA polymerase of *E. coli* was reported in previous research (74). This enzyme polymerizes the triphosphate side of the ribonucleic acid on a DNA template. Bacterial RNA polymerase is inhibited by a number of antibiotics, such as actinomycin and mitomycin.

Herbal Plants With Antimicrobial Activity in the North and East of Syria

Most of the world's population relies on traditional medicinal methods, and about 20 000 plant species are used medicinally worldwide (75). Table 1 presents the herbal plants that are used to treat human pathogenic microorganisms and their compounds with antimicrobial and antioxidant properties.

P-cymene, terpinene, caffeic acid, kaempferol, quercetin, capsaicin, 1,8-cineole, coumarin, flavonoids, tannins, rutin, gallic acid, alkaloids, vitamin C and E, fatty acids, and saponins have been reported as the most chemical constituents of the mentioned herbal plants. The antimicrobial properties of these herbal plants, mainly *E. coli*, *S. typhimurium*, *P. aeruginosa*, *C. albicans*, *S. aureus*, *K. pneumonia*, *S. listeria*, *B. cereus*, *L. monocytogenes*, and *B. subtilis*, have been reported as well.

Conclusion

Traditional medicine is an important method in the treatment of diseases because it uses plants that have biologically active compounds. In this study, important herbal plants with antimicrobial activities were selected in Syria, especially in the north and east of Syria. The herbal plants, including *Cuminum cyminum*, *Mentha piperita*, *Allium cepa*, *Majorana hortensis*, *Eucalyptus camaldulensis*, *Thymus capitatus*, *Achillea millefolium*, *Malva parviflor*, and *Capparis spinose*, have significant antibacterial and antifungal activities against pathogenic pathogens. This study also focused on the mechanisms of antioxidant activity and inhibition of microbial growth.

The resistance of pathogenic microorganisms to synthetic drugs, as well as the harmful effects of using these drugs, have urged researchers to look for herbal plants with medicinal properties to discover medicinal compounds in order to overcome these problems. Plants containing medicinal compounds and pathogenic microorganisms tested on these plants were reported in this review. Based on this research, compounds, including p-cymene, kaempferol, quercetin, capsaicin, 1,8-cineole, flavonoids, gallic acid, and alkaloids, as well as pathogens, including *E. coli*, *S. typhimurium*, *P. aeruginosa*, *C. albicans*, *S. aureus*, *K. pneumonia*, *S. listeria*, *B. cereus*,

Table 1. Herbal Plants With Chemical Compounds and Their Antimicrobial Activities

Scientific Name	Main Bioactive Compounds	Antimicrobial Activity	Reference
Cuminum cyminum	Cumin aldehyde, beta-pinene, p-cymene, and beta-terpinene	Bacteria: *S. aureus*, *Proteus vulgaris*, and *S. typhimurium*. Fungi: *Candida* spp., *Botrytis cinerea*, *Aspergillus niger*, and *Penicillium expansum*	(76)
Mentha piperita	Menthone, levomenthol, eucalyptol, 2-boranone, indoburnol, and linalyl acetate	Bacteria: *S. aureus, Streptococcus listeria*, and *Pseudomonas strains*	(77)
Allium cepa	Pectin, prostaglandins, lectins, fructans, adenosine, vitamins B1, B2, B6, C, E, and biotin	Bacteria: *B. cereus, S. aureus*, *Micrococcus luteus*, *Listeria monocytogenes*, *E. coli*, and *P. aeruginosa* Fungi: *C. albicans*	(78)
Zingiber officinale	Camphene, citral, zingiberene, ar-curcumene, geranial, and bisabolene	Bacteria: *Salmonella* spp., and *E. coli*	(79)
Coriandrum sativum	Gallic acid, quercetin, polyphenols, caffeic acid, kaempferol, and ellagic acid	Bacteria: *S. aureus,* *B. cereus, L. monocytogenes,* and *E. coli* Fungi: *C. albicans*	(80)
Majorana hortensis	Terpinen-4-ol, trans-sabinene, -terpinene, and α-terpinene	Bacteria: *Beneckea natriegens*, *Erwinia carotovora*, *Moraxella* sp., and *Aspergillus nigeria*	(81)
Petroselinum crispum	Apiol, myristicin, and phyllandrin	Bacteria: *S. aureus* and *L. monocytogenes*	(82)
Trigonella foenum-graecum	Steroidal saponin, galactomannan, and 4-OH isoleucine	Bacteria: *E. coli* and *S. aureus*	(83)
Eucalyptus camaldulensis	Pinene, 1,8-cineol, and trans-pinocarveol	Bacteria: *E. coli* and *Bacillus subtilis* Fungal: *Rhizopus stolonifer*	(84)
Pimpinella anisum	Trans-anito-estragole, beta-hemachalin, para-anisaldehyde, and methylcaffeicol	Bacteria: *S. aureus*, *S. typhimurium*, and *E. coli*	(85)
Thymus capitatus	P-cymene, γ-terpinene, and thymol	Bacteria: *P. aeruginosa*, *E. coli*, *L. monocytogenes*, *S. aureus*, and *Salmonella typhi*	(86)
Allium sativum	Allicin, alliin, diallyl sulfide, ajoene, and S-allyl-cysteine	Bacteria: *E. coli*, *L. monocytogenes*, *L. acidophilus*, *S. aureus*, *K. pneumoniae*, *Serratia marcescens*, *Clostridium difficile*, and *P. aeruginosa*	(87)
Capsicum annuum	Naringenin, caffeic acid, kaempferol, quercetin, capsaicin, disodium hydrocapsaicin, coumarin, and rutin	Bacteria: *S. aureus*, *S. Typhimurium*, and *P. aeruginosa*	(88)
Artemisia verlotiorum	α-thujone, 1,8-cineole, β-caryophyllene, and beta-thujone	Bacteria: *E. coli*, *S. pyogenes*, and *S. epidermidis*	(89)
Achillea millefolium	Isovaleric acid, salicylic acid, asparagine, sterols, flavonoids, myrrh, tannins, coumarin, and dihydro-a-cyclogeranyl hexanoate	Bacteria: *S. pneumoniae*, *Clostridium perfringens*, *C. albicans*, *Mycobacterium smear*, *Acinetobacter lwoffii*, and *C. krusei*	(90)
Malva parviflor	Phenols, flavonoids, saponins, alkaloids, resins, and tannins	Bacteria: *E. coli*, *S. aureus*, and *B. subtilis* Fungal: *A. niger* and *A. oryzae*	(91)
Urtica dioica	Flavonoids, kaempferol, phenolic acids, rutin, carotenoids, and vitamin A	Bacteria: *B. subtilis, L. plantarum, P. aeruginosa,* and *E. coli*	(92)
Rubus fruticosu	Gallic acid, epicatechin, ferulic acid, and quercetin	Bacteria: *B. cereus, B. subtilis, Streptococcus marcescens, S. aureus, M. luteus, Proteus mirabilis, B. subtilis*, and *P. aeruginosa*	(93)
Capparis spinosa	Flavonoids, genetic acid, terpenoids, cinnamic acid, vitamins C and E, iron, zinc, polysaccharides, alkaloids, benzoic acid, and volatile oils	Bacteria: *B. subtilis*, *K. pneumonia*, *Erwinia carotovora*, *E. coli*, and *C. albicans*	(94)
Arctostaphylos uva-ursi	Gallic acid, arbutin and hypericin, and arbutin phenol glycoside	Bacteria: *E. coli* and *Enterococcus faecalis*	(95)
Avena sativa	Tocopherols, tocotrienols, flavonoids, avenanthramides, and phenolic amides	Bacteria: *Gaeumannomyces graminis* and *Pratylenchus thornei*	(96)

Note. S. aureus: *Staphylococcus aureus*; *S. typhimurium*: *Salmonella typhimurium*; *B. cereus*: *Bacillus cereus*; *E. coli*: *Escherichia coli*; *P. aeruginosa*: *Pseudomonas aeruginosa*; *C. albicans*: *Candida albicans*; *L. monocytogenes*: *Listeria monocytogenes*; *L. acidophilus*: *Lactobacillus acidophilus*; *K. pneumoniae*: *Klebsiella pneumoniae*; *S. pyogenes*: *Streptococcus pyogenes*; *S. epidermidis*: *Staphylococcus epidermidis*; *S. pneumoniae*: *Streptococcus pneumoniae*; *C. krusei*: *Candida krusei*; *B. subtilis*: *Bacillus subtilis*; *A. niger*: *Aspergillus niger*; *A. oryzae*: *Aspergillus oryzae*; *L. plantarum*: *Lactiplantibacillus plantarum*; *M. luteus*: *Micrococcus luteus*.

L. monocytogenes, and *B. subtilis*, can be suggested for pharmaceutical and medical research in strategic projects in the north and east of Syria.

Overall, the results of this study support the idea that medicinal plants can be promising sources of potential anticancer, antimicrobial, and antioxidant agents and can also serve as a cornerstone for the selection of plant species in the discovery of new bioactive natural compounds in medicine and pharmacology fields.

Authors' Contribution

Conceptualization: Mostafa Alamholo.
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Competing Interests

The authors declare that there is no conflict of interest.

Ethical Approval

Not applicable.

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