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Review Article

Nitrofurans as Potent Antibacterial Agents: A Systematic Review of Literature

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Abstract

Introduction: Bacterial infection and the growing resistance of the bacteria to drugs is a global issue which challenges the health system. Therefore, the development of drugs with a different mechanism of action is a reasonable approach to overcome the drug resistance. Nitrofurans are antibacterial agents with broad-spectrum effects on various types of bacteria. In the present study, we aimed to review the reported derivatives of nitrofurans with antibacterial impacts to evaluate the potency and efficiency of these agents as candidates for antibacterial drug development.
Methods: A systematic literature search was performed on April 2021 in databases using "Nitrofurans" and "antibacterial" as the keywords using all their equivalents, similar terms, and known forms. The search was first limited to original articles in the English language, and all the relevant articles were included for data extraction. The main outcomes in all the included studies were antibacterial efficacy and bactericidal power.
Results: Overall, 36 articles were found and used for data extraction. Findings showed that nitrofuran-based compounds have satisfactory antimicrobial effects at the micromolar level. Most of these agents also revealed high efficacy on gram-positive and gram-negative bacteria with minimal toxicity on human cells. Findings suggested that chemical modification of nitrofurans with appropriate functional groups and molecules can enhance the efficiency of these agents.
Conclusion: According to the included studies, nitrofuran and its derivatives can be considered promising candidates for future drug discovery to combat drug-resistant

bacteria.

Keywords: Nitrofurans, Bacterial infection, Antimicrobial, Drug resistance.

1. Introduction

Bacterial infections with various antibiotic-resistant strains are increasing in the community, which has led to a global challenge. Bacteria excrete extracellular compounds including drugs, chemicals, and antibiotics, out of the cell and prevent the antibiotics from inhibiting bacterial growth. This process as a pump efflux, is fundamental in creating multidrug resistance and is one of the most important intrinsic antibiotic resistances in bacteria, as well. Bacterial resistance to antibiotics is based mainly on some mechanisms such as the production of drug-degrading enzymes, reduced drug permeability, changes in drug receptors at the bacterial level, and changes in the structure of the bacterial cell wall [1]. The drug resistance has redoubled the efforts to introduce antibacterial agents to overcome multidrug resistance and reduce the side effects of antibiotic therapy.

So far, many chemically synthetic and naturally occurring molecules and supermolecules with antibacterial effects have been introduced. Nitrofurans ($C_8H_6N_4O_5$) are synthetic chemotherapeutics with a broad spectrum of activity against most gram-positive and gram-negative bacteria, fungi, and protozoa. They are structurally composed of a furan ring containing a nitro group. To date, many nitrofurans with broad-spectrum antibacterial effects have been synthesized. They act through changes in the metabolic function of the bacteria by inhibiting the acetyl-CoA and thereby inhibiting glucose metabolism and energy production. Nitrofurans are widely used in animal husbandry and aquaculture to treat enteritis, acne, and ulcer disease caused by *Escherichia coli* or Salmonella [2]. They are also considered potent agents with promising antibacterial effects against various pathogenic bacteria such as *Micrococcus luteus*, *Staphylococcus aureus*, *Bacillus subtilis*, *Pseudomonas aeruginosa*, *Klebsiella planticola*, and *E. coli* [3].

Nowadays, research on nitrofurans has focused on designing and synthesizing hybrid complexes of these compounds to minimize the side effects and increase treatment efficiency. To better understand the efficacy and potential benefits of nitrofuran compounds, in the present study, all available literature reporting the antibacterial impact of nitrofurans and their derivatives were collected and reviewed.

2. Materials and Methods

2.1. Search method and eligibility criteria

A systematic literature search was performed on April 2021 on Web of Science, PubMed, Scopus, Ovid, and Google Scholar using “Nitrofurans” and “antibacterial” as the search keywords using all their equivalents, similar terms and known forms. We initially searched only original English articles, excluding review articles, conference papers, commentaries, and editorials. The collected articles were then reviewed, and relevant articles were used for data synthesis. Two authors searched and reviewed the titles, abstracts, and keywords of collected articles independently, and discussed the issue with the second author in case of uncertainty and disagreement. All the procedures, including literature search, article selection, and data extraction, were performed based on the

recommendation of PRISMA checklist 2009, as a known and standard protocol for reporting systematic reviews [4].

2.2. Data synthesis and the variables

Informative data for describing the included studies, such as author's name, type of microorganism, measured variables, and the conjugate part of nitrofurans were extracted. In addition, the half-maximal inhibitory concentration (IC50) was extracted and quantitatively described. The IC50 value was the most crucial outcome in the included studies. There are several significant variables.

3. Results

Considering the defined inclusion criteria, the literature search led to a total of 4541 articles, of which 2912 were from PubMed, 1561 were in Scopus, 67 were from the other databases and additional 12 articles were found in the reference list of included articles. After removing duplicated articles and the other irrelevant documents, 36 articles were collected which were used for data extraction. The article selection process is demonstrated in **Figure 1**.

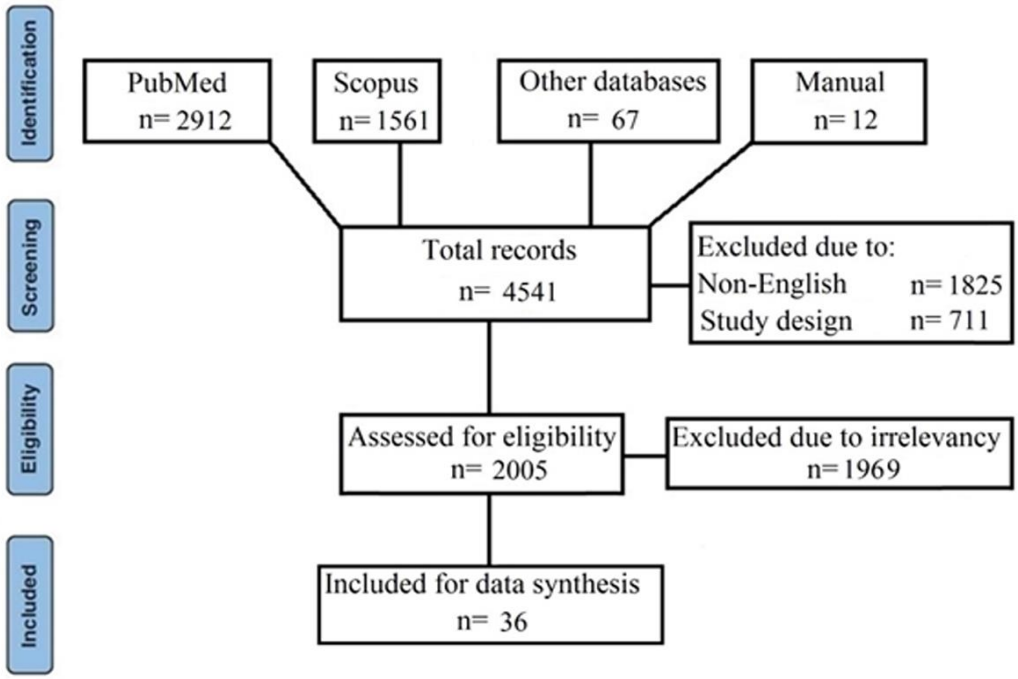

Figure 1. Article selection procedure

The results of included articles confirmed the effectiveness of nitrofuran and its derivatives as a potent antibacterial agent and indicatd the promising bacterial growth inhibition towards both gram-positive and gram-negative pathogenic strains. However, findings revealed mild inhibitory effects towards most gram-negative bacteria. In addition, some hybrid nitrofuran compounds exhibited remarkable antibacterial activity towards pathogenic *Micrococcus luteus*, *Staphylococcus aureus*, and *Bacillus subtilis* strains at micromolar level (0.8 µg/mL) [3]. According to the literature, some of these derivatives demonstrated significant antibacterial activities against various important pathogenic microbial strains such as *Neisseria gonorrhoeae*, and *S. aureus* comparable with Spectinomycin, as a conventional drug for the treatment

of bacterial infection. Chemical modification and the functional groups were shown to be the most determinant element in the biological activity of the compound. According to the findings of a study, developing nitrofuran analogs, such as chemical alteration of nitrofuran molecules, can boost the nitrofuran-activating reductase enzyme in bacteria, which is a novel technique for combating drug resistance [2]. In addition, the in vivo efficacy of nitrofuran compound demonstrated promising bacteriostatic activity, suggesting that these molecules could be considered as novel antimycobacterial agents. Many of the newly synthesized compounds also showed no considerable cytotoxicity towards human cell lines at concentrations up to 100 μM [5]. A summary of studies and related data are presented in **Table 1**.

Table 1. Studies and related data on the conjugated part of nitrofuran-based compounds

NO	Reference	Variable	Conjugate part	Target (bacteria type)	Inhibition value (IC50)
1	Le, *et al*. 2019 [2]	antimicrobial	5-Nitrofuran	*E. coli*	2 μg/mL
2	Gallardo-Macias, *et al*. 2019 [6]	Antitubercular l	N-benzyl-5-nitrofuran-2-carboxamide	*M. tuberculosis H37Rv*	0.019-0.20 μM
3	Pandolfi, *et al*. 2019 [7]	Antifungal effect	Amine and amide indole derivatives	*C. albicans strains, G. mellonella*	500-1000 (μg/mL)
4	Krasavin, *et al*. 2019 [5]	Antimycobacterial effect, drug sensitivity	5-nitrofuroyl moiety	*M. tuberculosis*	100(μM)
5	Fan, *et al*. 2018 [8]	Antimycobacterial, antitubercular activities	nitrofuranylamides	*Tuberculosis,* MTB H37Rv	1(mg/mL)
6	Phillips, *et al*. 2018 [9]	Antibacterial	*N*-Substituted-(*d*-/ *l*-Alaninyl) 1 *H*-1,2,3-Triazolylmethyl Oxazolidinones	*S. aureus, S. epidermidis, E.s faecalis, M. catarrhalis*	2(g/mL)
7	Krasavin, *et al*. 2018 [10]	Antimycobacterial effect, drug resistance	5-nitrofuran-2-oyl moiety	*M. tuberculosis* H37Rv strain	0.8(μg/mL)
8	Huttner, *et al*. 2018 [11]	Antibacterial	5-Day Nitrofurantoin	*E. coli, Klebsiella*	-
9	Picconi, *et al*. 2017 [12]	Antimicrobial	5-nitrofuran	*S. aureus, S. pyogenes, E. coli, P. aeruginosa, S. typhimurium*	10 (pg/mL)
10	Picconi, *et al*. 2017 [13]	Antibacterial	nitrofuranyl isoxazolines	*Staphylococcus strains*	4-32 (μg/mL)
11	Verbitskiy, *et al*. 2017 [14]	Antibacterial activities	5-aryl-4-(5-nitrofuran-2-yl)-pyrimidines	*M. tuberculosis, N. gonorrhoeae, S. aureus, C. difficile, S. pneumoniae, Klebsiella species,*	1.5>250 (μg/mL)

				Acinetobacter, Campylobacter and *Salmonella.*	
12	Arias, *et al*. 2017 [15]	Antiparasitic activity, Enzyme inhibitory effect	5-nitro-2-furoic acid	*Trypanosomatids*	24 (mM)
13	Gould, *et al*. 2017 [16]	Antimycobacterial	tetrahydrothieno[2, 3-c]pyridine-3-carboxamide	*M. tuberculosis*	9.28 (μM)
14	Ran, *et al*. 2016 [17]	Antitubercular and antibacterial activity	2-aminothiazole conjugated nitrofuran	*M. tuberculosis* and *Staphylococcus*	0.27 (μg/mL)
15	Abdel-Aziz, *et al*. 2015 [18]	trypanocidal activity	bis-tetrahydropyran 1,4-triazole analogues	*T. brucei, T. cruzi and L. major*	4.5 (μg/mL)
16	Pieroni, *et al*. 2015 [19]	Antitubercular	2,4-diphenyl-1H-imidazoles	*M. tuberculosis*	-
17	Samala, *et al*. 2014 [20]	antibacterial	[1,2,4]triazolo[3,4-b][1,3,4]thiadiazines and [1,2,4]triazolo[3,4-b][1,3,4] thiadiazoles	*S. aureus, E. coli*	12.5 (μg/mL)
18	Zorzi, *et al*. 2014 [21]	antimicrobial	5-nitrofuran	*S. aureus, E. coli, E. faecalis*	4.8–2.4 (μg/mL)
19	Asadipour, *et al*. 2013 [22]	antibacterial	2-Alkylthio-5-(nitroaryl)-1,3,4-thiadiazole	*H. pylori*	12.5-100 (μg/disk)
20	Kamal, *et al*. 2013 [3]	Bacterial growth inhibition	5-nitrofuran-triazole	*M. luteus, S. aureus, Bacillus subtilis, E. coli, Pseudomonas aeruginosa, Klebsiella planticola*	1.17 (μg/mL)
21	Phillips, *et al*. 2013 [23]	Antibacterial activities, panel of susceptible and resistant	N-substituted-glycinyl 1H-1,2,3-triazolyl oxazolidinones	*Methicillin-susceptible S. aureus, methicillin-resistant coagulase-negative staphylococci, methicillin-sensitive coagulase-negative staphylococci, vancomycin-sensitive enterococci, E. coli, H. influenza, M. catarrhalis*	0.25-1 (μg/mL)
22	Lapa, *et al*. 2013 [24]	Antibacterial	3-amino-1H-pyrazolo[3,4-b]quinolines	*Streptomyces*	>64 (μg/mL)
23	Yanagita, *et al*. 2012 [25]	Antimicrobial and	5-Nitrofuran-2-yl Hydrazones	*A. fumigates, S. aureus, S. pneumonia,*	0.12-7.81 (μg/mL)

		Antitubercular		*B. subtilis, S. typhimurium, K. pneumonia, E. coli, M. tuberculosis.*	
24	Badr, 2011 [26]	antiviral	5-nitrofuran-2-yl)-7H-[1,2,4]triazolo[3,4-b][1,3,4]thiadiazines	*S. aureus*	0.1 to 70 (µg/mL)
25	Soares de Oliveira, *et al*. 2011 [27]	antibacterial	1,4-diphenyl-5-(5-nitro-2-furanyl)-1,3,4-thiadiazolium-2-thiol chloride (MC-1) and 4-phenyl-5-(5-nitro-2-furanyl)-1,3,4-thiadiazolium-2-phenylamine chloride (MC-2)	*S. aureus*	16 (µg/mL)
26	Blackburn, *et al*. 2010 [28]	Antibacterial activities	N-acyl and N-aroylpyrazolines	*Escherichia, Enterococcus, Staphylococcus*	<1 (µM)
27	Kamal, *et al*. 2010 [29]	Anti-tubercular effect, microbial sensitivity	Benzothiadiazine 1,1-dioxide	*S. aureus, S. epidermidis, B. subtilis, E. coli, K. pneumoniae, P. aeruginosa.*	2 (mg/mL)
28	Ancizu, et al. 2009 [30]	Antimicrobial	1,4-di-N-oxide	*M. tuberculosis, T. cruzi*	25 (µM)
29	Al-Saadi, *et al*. 2008 [31]	antibacterial and antifungal	2,4,5-trisubstituted thiazole	*S. aureus, B. subtilis, B. cereus, E. coli, P. aeruginosa*	6.25-12.5 (µg/mL)
30	Kamal, *et al*. 2007 [32]	antimycobacterial	nitroheterocyclic-based 1,2,4-benzothiadiazines	*M. tuberculosis H37Rv, S. aureus E. coli P. aeruginosa, B. Subtilis*	100 (µg/mL)
31	Metwally, *et al*. 2006 [33]	Antimicrobial, antifungal	2-aryl-quinoline-4-carboxylic acid	*Staphylococcus, E.coli, C. albicans*	12.5-25 (µg/mL)
32	Chadfield and Hinton 2003 [34]	Antibacterial	2-methyl-5-nitrofurans	*E. coli, S. aureus*	31.2 to 62.5 (mg/L)
33	Jones Jr and Daly 1993 [35]	Antibacterial	5-nitro-2-furaldehyde	*E. coli, P. aeruginosa, P. mirabilis, Serratia*	8.0 (pg/mL)
34	Kupchik, *et al*. 1982 [36]	antifungal agent, Antimicrobial	triorganotin 5-nitro-2-furoates	*A. niger, C. globosum, C. carpophilum, F. rnoniliform, M. verrucaria*	100 (µg/mL)
35	Roveri, *et al*. 1982 [37]	Antimicrobial	Prophylaxis with nitrofurans	*Salmonellae*	16 (µg/mL)
36	Gadebusch and Basch 1974 [38]	Antibacterial, antifungal, and antiprotozoal	Trans-5-amino-3-[2-(5-nitro-2-furyl)vinyl]-delta2-1,2,4-oxadiazole	*S. aureus, E. coli, S. schottmuelleri, S. flexneri, C. albicans, T. foetus*	10 (µg/mL)

4. Discussion

Nitrofuran and its derivatives are a known class of antibacterial agents, commonly used to treat bacterial skin infections, urinary tract infections, and an antiparasitic drug. They are thought to act through binding to various targets, including DNA, enzymes, and transporters. Glutathione reductase, xanthine dehydrogenase/oxidase, and NADPH-cytochrome P450 reductase are the most important targets of nitrofuran derivatives. Although the exact mechanism of action has not been determined, the mechanism of action of these drugs is based on the inhibition of DNA polymerase and topoisomerase. Also, the antibacterial effect of these agents is suggested to be due to the reduction products derived from degradation of the drug, which is mediated through acting on bacterial nitroreductase enzymes [2]. These highly reactive electrophilic products can interact with the DNA. These reduced intermediates of nitrofurans can prevent protein synthesis through binding to bacterial ribosomes [39]. Another known mechanism of antibacterial activity by these products is the prevention of mRNA translation due to disruption of codon–anticodon interactions.

The results of the present literature review showed that nitrofurans and its conjugated complexes have strong antibacterial effects, and depending on the conjugated part, the bactericidal power may differ. The results of a study demonstrated that placing the N-[5-(5-nitro-2-thienyl)-1,3,4-thiadiazole-2-yl] on the piperazine ring of quinolones can increase the antibacterial potency of nitrofuran complex (2). Furthermore, it was revealed that different conjugated groups might act on various strains. According to findings, the nitroaryl thiadiazide derivatives of nitrofuran had strong antibacterial effects against gram-positive bacteria, but no significant effects were observed against gram-negative bacteria. In addition to increasing nitrofuran derivative's antibacterial effects, nitroaryl attachment also increases the antibacterial activity of 1,3- and 4-thiodiazole (3). The complexation of nitrofurans with benzothiazole has also led to an increased potency against a variety of important pathogenic. Broad-spectrum antimicrobial effects of these compounds have received much attention in recent years, and many derivatives of this family have indicated significant inhibitory effects on bacteria such as *Bacillus cereus*, *Listeria monocytogenes*, *Escherichia coli*, and *Salmonella typhimurium* (4). Moreover, the derivative containing a thioamide branch (S═C-NH2) on the thiazole ring has a greater spectrum of action and inhibitory power. Thioamide is a biologically active component with antibacterial effects and plays an important role in Prothionamide, a drug used against tuberculosis-producing mycobacteria. Also, elimination of the methyl group was shown to reduce the antibacterial effects of methyl-containing nitrofuran derivative 30243589.

Nitrofuran derivatives are quickly absorbed from the gut and almost 40–50% is rapidly eliminated from the urine. However, these compounds have been associated with various side effects on the central nervous system and digestive system. The most common complications include ascending neuropathy, dizziness, drowsiness, headache, peripheral neuropathy, and gastrointestinal disturbances such as abdominal pain, anorexia, diarrhea, nausea, vomiting, and hepatopathy [40]. They may interfere with some drugs and antagonize the effects and reduce the effectiveness of these drugs. Likewise, because nitrofurans and their metabolites are carcinogenic and teratogenic to humans, their use is prohibited in some countries

in livestock, poultry, and animal feed. Taken together, compared with other antimicrobial agents, nitrofuran and its derivatives cannot be considered as potent antibacterial agents; however, the conjugation of nitrofurans with the other agents may enhance the antibacterial activity and improve the safety of these compounds. On the other hand, it is worth noting that most nitrofurans compounds are no inferior to first-line antimicrobial agents and maybe even less toxic than some widely used antibacterial drug such as Ciprofloxacin, which could be a starting point for future drug optimization [3, 8]. Furthermore, findings have shown low toxicity and similar efficacy with most conventional drugs such as etambutol for nitrofuran-based compounds in animal models of drug-resistant tuberculosis [10].

The results suggest that the novel scaffolds of nitrofuran conjugates may be a promising class of potent antimicrobial agents [17]. Pharmacological stimulation and docking analysis have also revealed that some nitrofuran compounds, as inhibitors of enzymes such as trypanothione reductase, bind to the enzyme-substrate complex, and inhibit bacterial growth [15]. Findings have shown that most of the reported side effects associated with nitrofuran compounds are mainly due to the weak hydrosolubility, which can be improved by introducing hydrophilic groups to the structure furan ring. Modulation and chemical modification of the nitrofuran moiety, such as attaching methoxy-carbonyl and methoxy groups to the nitrofuran ring can result in a drastic change in inhibitory potency [25]. On the other hand, the substitution of guanidino at the 4N-piperazine position or conversion of the ester linkage and substitution of the amine group or aromatic ring was shown to result in a significant decrease in antibacterial activity [24]. However, D- or L- isoforms of the compounds do not seem to be effective in the antibacterial activity of nitrofuran derivatives. Since much more modification can be performed on nitrofuran moiety, further chemical alteration with potent antimicrobial agents such as antimicrobial peptides or other biologically active molecules may lead to the development and enhancement of nitrofuran-based compounds to increase potency and specificity to target bacteria [9].

5. Conclusion

The findings of this study offer a fresh perspective on creating antibacterial drugs to combat drug-resistant microorganisms. Chemical modification of nitrofuran is a viable technique for generating novel derivatives to minimize side effects and improve the inhibitory effect of nitrofuran-based drugs, according to the findings of investigations. Furthermore, strong bactericidal potency and low cytotoxicity toward human cells have been demonstrated that making these compounds is a suitable contender for future therapeutic development.

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Conflict of interest

The authors declares no conflict of interest.

Consent for publications

The authors declare, read, and approve the final manuscript for publication.

Availability of data and material

The authors declare that they embedded all data in the manuscript.

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