Piperidine is a saturated heterocyclic ring, considered as a privileged scaffold in view of its role in a wide range of biological activities. Piperidine is a five-membered ring with nitrogen at the 2-position, which is known for its planar nature and ability to form stable conjugated systems. Antioxidant activity of piperidine is due to its ability to inhibit or quench free radicals (hydroxyl and peroxyl radicals). Piperine is piperidine containing alkaloid, present in pepper extracts, which is a well-studied and recognized natural antioxidant.

**ABSTRACT**

Piperidine is a saturated heterocyclic secondary amine which is associated with a diverse set of biological activities such as antimicrobial, anti-inflammatory, antiviral, antimalarial, general anesthetic, antidepressant, antitumor, antiepileptic, antithyroid, antitumor, anticonvulsant, antiproliferative, antiplatelet, anti-inflammatory, antihypertensive, hepatoprotective, antidiabetic, and antihyperlipidemic activities. Piperidine is a highly versatile heterocyclic ring considered as a privileged scaffold due to its role in various biological activities. Piperidine and its derivatives are widely used in medicine, agrochemicals, and pharmaceutical industries.

**INTRODUCTION**

Piperidine is a five-membered ring system containing a nitrogen atom at the 2-position. It is a privileged scaffold in the field of drug discovery due to its versatile chemical properties and diverse biological activities. Piperidine-based compounds display a wide range of activities such as antimicrobial, anti-inflammatory, antitumor, anticonvulsant, antithyroid, and antimalarial activities.

**REVIEW ON ANTIoxidANT AND RELATED BIOLOGICAL ACTIVITIES OF PIPERIDINE CONTAINING COMPOUNDS**

**Naturally occurring piperidine-based compounds**

Piperine is piperidine containing an alkaloid, present in pepper extracts, and is considered as a privileged scaffold in the field of drug discovery. Piperine is a known inhibitor of the activity of various enzymes, including carbonic anhydrase, lipid peroxidation, and oxidant stress. Piperine is often used as a natural antioxidant and has been reported to exhibit strong antioxidant activity.

**Synthetic piperidines**

The compounds were classified into piperidine nitroxides, substituted piperidines, N-acyl substituted piperidines, diaryl-substituted piperidinones, Piperidine oximes, and piperidine hydrazides. Piperine nitroxides are potent antioxidant agents due to their ability to scavenge reactive free radicals. AK-13 and AK-14 were evaluated for their antioxidant activity using DPPH assay. These compounds showed potential antioxidant activity due to their ability to scavenge reactive free radicals.

**Substituted piperidines**

Frietas et al. evaluated the in vitro antioxidant activity of 12-(2R, 5R, 6R)-5-hydroxy-6-methyl piperidin-2-one (iso-6-cassine) by determining the activity of glutathione-S-transferase, catalase, glutathione peroxidase, and lipid peroxidation. The obtained results demonstrated that the synthesized compounds had potential antioxidant activity.

**Keywords:** Piperidine nitroxides, Substituted piperidines, Unsaturated piperidines, N-acyl substituted piperidines, Diaryl substituted piperidinones, Piperidine oximes, Piperidine hydrazides.

© 2018 The Authors. Published by Innovare Academic Sciences Pvt Ltd. This is an open access article under the CC BY license (http://creativecommons.org/licenses/by/4.0/) DOI: http://dx.doi.org/10.22159/ajpcr.2018.v11i8.26536
Alexidis et al. synthesized different piperidine derivatives (Fig. 7) by introducing several substituent groups with chelating properties. Cysteamine derivatives exhibited potent antioxidant activity in the assays such as lipid peroxidation inhibitory assay, hydroxyl radical scavenging assay, and DPPH assay due to oxidizable SH group. The derivatives in which SH group was replaced by hydroxy and amine functionality, showed poor antioxidant activity. The lipid peroxidation inhibition was time and concentration dependent [18].

Kiasalari et al. prepared phenylcyclidine (PCP) and its analog 1-[1-(3-methoxyphenyl) (tetralyl)] piperidine (PCP1) (Fig. 8) by introducing phenyl cyclohexyl ring and 1-(2-methoxyphenyl)-1, 2, 3, 4-tetrahydronaphthalene ring at piperidine nitrogen. Antioxidant activity of PCP and PCP1 was evaluated using malondialdehyde, nitric oxide (NO), and superoxide dismutase (SOD) assessment and their anticonvulsant effect was studied using pentylentetrazole-induced kindling model. The results showed that PCP1 exhibited marked antioxidant and anticonvulsant activity when compared to PCP [5].

Different derivatives of ethyl N-aryl-2,6-dioxo-piperid-3-ene-4-carboxylates (Fig. 9) were synthesized and screened for their antioxidant and antimicrobial activities. Aryl groups possessing electron donating/withdrawing groups were introduced on the nitrogen of ethyl 2,6-dioxo-1,2,3,6-tetrahydropyridine-4-carboxylate. Among the synthesized compounds, derivatives with unsubstituted phenyl ring and 4-nitro substituted phenyl ring showed highest DPPH free radical scavenging activity. Most of the compounds showed moderate antioxidant and antimicrobial activities [19].

A series of piperidine sulfonamide derivatives (Fig. 11) were synthesized by coupling of different sulfonyl chlorides with 4-{piperidin-1-yl} aniline. Antioxidant activity was evaluated using DPPH assay. Enzyme inhibitory activities were screened using butyrylcholinesterase, lipoxygenase, and acetylcholinesterase enzymes. N-[4-{4-(piperidin-1-yl) acetamido} benzene sulfonamide demonstrated good scavenging activity in DPPH assay. This study also concluded that the unsubstituted derivative can be a potent molecule for the treatment of Alzheimer’s disease, cancer, inflammation, and bronchial asthma [21].

![Fig. 1: Clinically available piperidine containing drugs](image1)

![Fig. 2: Naturally occurring compounds bearing piperidine ring](image2)

![Fig. 3: Structures of 2, 2, 6, 6-Tetramethylpiperidin-1-yl) oxyl, 2, 2, 6, 6-tetramethyl-4-piperidinol-N-oxyl (TEMPO) and Mito TEMPOL](image3)

![Fig. 4: 3, 4, 5-trisubstituted piperidines](image4)
A series of alkyl piperidines (Fig. 12) were synthesized using piperidine-2-methanol and piperidine-2-ethanol as parent structures and screened for their antioxidant, antibacterial, and antifungal activities. It was observed that a compound possessing fluoro group at para position demonstrated good antioxidant, antibacterial, and antifungal activities. Results concluded that good antioxidant activity of the active compounds was due to the presence of halogens fused with methanol group [22].

A novel series of nitrogen-containing (piperidine, morpholine, and N-methyl piperazine) benzophenone analogs (Fig. 13) were synthesized by Mannich reaction. The compounds elicited inhibitory activity against tumor necrosis factor-α (TNF-α), interleukin-6 (IL-6) cytokines and found to be active in DPPH assay. Piperidine substituted compounds showed good antioxidant activity and also elicited 20–100% TNF-α inhibition at 10 µM and 83–100% IL-6 inhibition at 10 µM, respectively [23].

Unsaturated piperidine derivatives
A series of piperidine containing derivatives (Fig. 14) were synthesized, where nitrogen is substituted with an acetyl group. These derivatives were screened for antioxidant (DPPH and SOD assays) and antimicrobial activities. Among all, 1-Adamantylthio derivative bearing methyl group demonstrated potent antioxidant activity (in both the assays) and antimicrobial activity [24].
Piperidine derivatives [unsaturated at 3 and 4 positions] (Fig. 15) were synthesized, and their antioxidant and antimicrobial activities were evaluated. Among the synthesized derivatives, derivative bearing methoxy substituent at R_3 and R_8 positions showed highest DPPH free radical scavenging activity whereas compound possessing cyano group at R_2 position showed poor scavenging activity. Antibacterial activity was evaluated using agar disc diffusion method, in which compound containing trifluoromethyl group at R_3 and R_8 positions showed poor antibacterial activity and the compound which contains cyano group at R_2 position showed potent antibacterial activity [25].

N-acyl substituted piperidines

Piperamide derivatives (Fig. 16) were synthesized by treating different piperazine and piperidine compounds with (E)-3-[7-methoxybenzo[d][1,3]dioxol-5-yl]acrylic acid. The compounds were evaluated for their antibacterial, antifungal (disc diffusion method), antidepressant (forced swim test and tail suspension test), antioxidant (DPPH and superoxide radical scavenging method) activities and also for their monoaminooxidase A and B inhibitory activity. Among the synthesized piperamides, the one possessing hydroxyl group on 4th position of piperidine ring showed highest antioxidant capacity, whereas 4-phenyl substituted piperidine derivative exhibited poor antioxidant activity indicating that this substitution is unfavorable for the activity [4].

Piperamide derivatives (Fig. 17) were synthesized using different substituted cinnamic acids. The prepared compounds were evaluated for their antibacterial and antioxidant (using DPPH and H_2O_2 radical scavenging assay) activities. Significant antioxidant and antibacterial activities were noticed for methoxy containing piperamides. Among all the prepared derivatives, derivative bearing chloro group on phenyl ring demonstrated promising antifungal activity [26].

6-Fluoro-3-(piperidin-4-yl)benzo[d]isoxazole derivatives (Fig. 19) were synthesized and evaluated for their antioxidant and antimicrobial activities. Compounds were evaluated for their antioxidant efficacy in H_2O_2 and DPPH methods. Among all, derivatives with electron withdrawing groups (F, Cl) exerted good antioxidant and antimicrobial activities [28].

Piperidine conjugated benzoxazole derivatives (Fig. 20) were synthesized and screened for their antioxidant, antibacterial, and anti-inflammatory activities. The results indicated that compounds bearing electron donating groups such as OCH_3, CH_3 groups exerted good inhibitory activity in DPPH, hydroxyl, and superoxide anion radical scavenging assays, while compounds with dinitro substituents exhibited highest antibacterial activity, compounds with nitro group...
showed highest anti-inflammatory activity in both phospholipase A2 and lipoxygenase inhibition assays [29]. By replacing sulfonyl group with carbonyl moiety, authors further synthesized several benzisoxazole derivatives (Fig. 20) and determined their antioxidant, antibacterial, and anti-inflammatory activities.

Methyl and methoxy substituted derivatives displayed good antioxidant activity against DPPH, superoxide anion, and hydroxyl radical scavenging assays. Antibacterial activity was evaluated using disc diffusion method, in which compound with unsubstituted phenyl ring exhibited highest antibacterial activity. The derivatives containing 4-methyl or 2/4-nitro group showed good anti-inflammatory activity [30].

**Diaryl substituted piperidinones**

Piperidinone based compounds, especially substituted with aryl rings at C2 and C6 positions display promising antioxidant activities. Ajay et al. recently reviewed various synthetic procedures and biological activities of diaryl substituted piperidinones [31]. The antioxidant potential of 3-benzylidene-5-methyl-2,6-diaryl piperidin-4-ones (Fig. 21) was studied using DPPH assay. In the tested compounds (Z)-3-(4-chlorobenzylidene)-2,6-bis (4-chlorophenyl)-5-methyl piperidin-4-one and (Z)-3-(3-nitrobenzylidene)-5-methyl-2,6-bis(3-nitrophenyl) piperidin-4-one (Fig. 21) were found to be more active when compared to ascorbic acid. Authors mentioned that electron-donating nature of the substituents such as hydroxy or methoxy groups on 3-arylidene-4-piperidones might be responsible for antioxidant activity [32].

Substituted piperidines and their respective alcohols (Fig. 22) were synthesized and evaluated for their antioxidant activity. Piperidiones showed a highest antioxidant effect when compared to the isomeric alcohols [33].

A series of 4-methyl-N’-(3-alkyl-2,6-diaryl piperidin-4-ylidene)-1,2,3-thiadiazole-5-carboxhydrazides (Fig. 23) were synthesized and evaluated for their antioxidant, antimicrobial, and anticancer activities. Antioxidant activity was evaluated by DPPH, ABTS, superoxide, hydroxyl, and NO free radical scavenging assays. Compounds possessing electron donating groups (methoxy and methyl) at para position of phenyl ring exhibited significant free radical scavenging activity. Compounds possessing electron withdrawing groups such as fluoro or chloro or bromo groups at para position of phenyl ring which is attached to piperidone ring at C2 and C6 positions, displayed promising antioxidant and antimicrobial activities [6].

**Piperidinone oximes**

A series of novel 2,6-diphenyl-3-alkylpiperidin-4-one-O-[2,4,6- tritertiary butyl cyclohexa-2-5-dienon-4-yl] oximes (Fig. 24) were synthesized, and their antioxidant and antimicrobial activities were screened. Most of the compounds were effective free radical scavengers in DPPH, superoxide, NO, ABTS, and hydroxyl assays. Compound with the electron releasing ethyl group exhibited promising antioxidant activity when compared to other compounds. Results showed that the compound possessing ethyl group at 3rd position on piperidine moiety showed potent antioxidant and antifungal activities [34].

Substituted piperidine oximes were synthesized and evaluated for their antioxidant (DPPH and superoxide free radical scavenging assays) and anti-inflammatory (carrageenan-induced rat paw edema) activities. 3,3-Dimethyl 2,6-dimethyl piperidine 4-one oxime (Fig. 25) exerted potent antioxidant activity. The active compound also displayed marked anti-inflammatory activity comparable to standard drug dexamethasone [35].

Harini et al. synthesized various piperidinone oxime esters (Fig. 26) and screened in vitro antioxidant and antimicrobial activities. Results showed that antioxidant activity was (DPPH assay, ABTS radical scavenging assay, FRAP assay, and cupric ion reducing antioxidant capacity assay) enhanced when the hydroxy group was introduced on the phenyl ring. Among the synthesized compounds, compounds with electronegative fluoro or chloro or bromo group on benzoyl ester moiety showed excellent antibacterial activity whereas compound with the fluoro group exhibited significant antifungal activity [36].

Harini et al. synthesized piperidinone oxime esters by replacing 4-methoxy phenyl ring with vanillin moiety few (Fig. 27) and screened their antioxidant activity. Compounds bearing hydroxy groups on...
phenyl ring demonstrated potent antioxidant activity. Compounds possessing fluoro or chloro group displayed good antibacterial and antifungal activities [37].

Further, thiazole-based piperidinone oximes were synthesized by the same research group, and their antioxidant and antimicrobial activities were evaluated. Among all, 2,6-bis(4-hydroxy-3-methoxyphenyl)-1-methylpiperido-4-one O-(2-(2-(4-hydroxy-3-methoxybenzylidene)hydrazinyl)thiazol-4-yl) oxime...
Piperidine hydrazides

Sulfonylhydrazones bearing piperidine derivatives (Fig. 29) were synthesized by condensing benzene sulfonylhydrazides with 2, 6-diphenyl piperidin-4-one and ethyl 4-oxopiperidine-1-carboxylate. Antioxidant and anticholinesterase activity of the compounds was evaluated, and their structural activity relationship was investigated.

Compound possessing methoxy derivative showed good antioxidant activity in CUPRAC assay. Compound substituted with bromo group showed highest antioxidant activity in DPPH, linoleic acid assays and exhibited potent activity in anticholinesterase inhibitory activity [39].

Miscellaneous

Imine substituted hindered piperidine stabilizers (Fig. 30) were synthesized, and their thermal and light stabilizing action was compared. The imine stabilizer structure is based on 2-hydroxy benzophenone and a 4-amino-tetramethyl piperidine structure. The polymer oxidation rate was determined by carbonyl index using Fourier-transform infrared spectroscopy (Fourier-transform infrared spectroscopy), and its hydroperoxide formation was measured. Most of the compounds were highly effective thermal and light stabilizers for polyolefin films and also inhibited the formation of hydroperoxide during thermal aging in polymers [40].

Plant-derived and synthetic piperidines are extremely important for their antioxidant properties [41-43]. For example, naturally occurred piperidine alkaloids demonstrated promising bactericidal, anticancer, and antioxidant properties [44]. The marked relationship between antioxidant properties and life-threatening diseases such as cancer highlight the significance of piperidines in the current drug research.

AUTHOR’S CONTRIBUTIONS

Manjusha RK and Shaheen Begum collected the articles and drafted the manuscript. Arfa Begum reviewed and drafted the article. Bharathi K supervised the review work. All authors discussed and finalized the manuscript.

CONFLICTS OF INTEREST

None.

REFERENCES

1. Kumar D, Singh V. Study of heterocyclic compound piperidine. Int J Res Sci Tech 2014; 3:25-8.
2. Przedborski S, Jackson-Lewis V, Djdetteti R, Liberatorre G, Vila M, Vukosavic S, et al. The parkinsonian toxin MPTP: Action and mechanism. Restor Neurol Neurosci 2000; 16:135-42.
3. Aridoss G, Partiban P, Ramachandran R, Prakash M, Kabilan S, Jeong YT, et al. Synthesis and spectral characterization of a new class of N-(N-methyl)piperazinoacetyl)-2,6-diarylpiperidin-4-ones: Antimicrobial, analgesic and antipyretic studies. Eur J Med Chem 2009; 44:577-92.
4. Prashanth MK, Revanasiddappa HD, Lokanatha Rai KM, Veeresh B. Synthesis, characterization, antidepressant and antioxidant activity of novel piperamides bearing piperidine and piperazine analogues. Bioorg Med Chem Lett 2012;22:7065-70.
5. Kiasalari Z, Khalili M, Roghani M, Ahmadi A, Mireie M. Antioxidant and antiepileptic activity of 1-[1-(3-Methoxyphenyl) (Tetrayl)] piperidine as a new derivative of phenylcyclene on pentylenetetrazole-induced kindling mice. Iran J Pathol 2013;9:138-48.
6. Paulrasu K, Arul D, Manikandan P, Amirthaganases S, Kuppasamy M, Balasankar T, et al. Synthesis of 4-methyl- N-(3-alkyl-2r,6C-diaryl piperidin-4-ylidene)-1,2,3-thiadiazole-5-carboxyhydrazides with antioxidant, antitumor and antimicrobial activities. Org Biomol Chem 2014;12:5911-21.
7. Frietas RM, Silva FO, Silva MG, Feng D. Antioxidant mechanisms of iso-cassine in suppressing seizures induced by pilocarpine. Braz J Pharmacol 2011;21:437-43.
8. Partiban P, Aridoss G, Rathika P, Ramkumar V, Kabilan S. Synthesis, stereochemistry and antimicrobial studies of novel oxime ethers of aza/diazbicycles. Bioorg Med Chem Lett 2009;19:6981-5.
9. Baumann M, Baxendale IR. An overview of the synthetic routes to the best selling drugs containing 6-membered heterocycles. Beilstein J Org Chem 2013;9:2265-319.
10. Mandary E, Francis RR, Ali HM, Sarwat MI, El Hady S. Antioxidant and structure-activity relationships (SARs) of some phenolic and anilines compounds. Ann Agric Sci 2013;58:173-81.
11. Hayathshami V, Vaseghi G, Pourfarzam M, Abdollahi A. Are antioxidants helpful for disease prevention? Res Pharm Sci 2010;5:1-8.
12. Marambaud P, Zhao H, Davies P. Resveratrol promotes clearance of Alzheimer’s disease amyloid-beta peptides. J Biol Chem 2005;280:37377-82.
13. Moon JK, Shibamoto T. Antioxidant assays for plant and food components. J Agric Food Chem 2009;57:1655-66.
14. Nakatani N, Inatani R, Oht a, Nishioka A. Chemical constituents of peppers (Piper spp.) and application to food preservation: Naturally occurring antioxidant compounds. Environ Health Perspect
Antibacterial and antioxidant activity evaluation of novel benzisoxazole derivatives as antimicrobial and antioxidant agents. Eur J Chem 2013;4:402-7.

Shivaprasad CM, Jagadish S, Swareo TR, Mohan CD, Roopashree R, Rangappa KS, et al. Synthesis of new benzisoxazole derivatives and their antimicrobial, antioxidant and anti-inflammatory activities. Eur J Chem 2013;5:91-5.

Kumar KA, Pavithra G, Renuka N, Kumar GV. Piperidine analogs: Synthesis and their diverse biological applications. Int J Pharm Pharm Sci 2012;2:145-54.

Nithya P, Madhuvi C. Antioxidant activity of 3-arylidene-4-piperidones in the 1,1-diphenyl-2-picrylhydrazyl scavenging assay. J Taibah Univ Sci 2017;11:40-5.

Karthik N, Nithiya S, Jayabharathi J. Novel piperidone derivatives: Synthesis, spectral and evaluation of antioxidant activity. Int J Drug Dev Res 2011;3:122-7.

Premalatha B, Elavarasan S, Bhakiaraj D, Chellakkil B, Gopalakrishnan M. Synthesis, antimicrobial and antioxidant activity of novel 2,6-diphenyl-1-3-alkylpiperidin-4-one-O(2,4,6-trinitrobenzyl)-cyclohexa-2,5-dienon-4-yloximes. J Appl Chem 2013;2:1509-15.

Tharini K, Sangoojha P. Antioxidant and anti-inflammatory activity of 3,3-dimethyl 2,6-dimethyl piperidine-4-one oxime. Int J Chem Sci 2015;13:1794-804.

Harini ST, Kumar HV, Peethambhar SK, Rangaswamy J, Naik N. Novel 2,6-bis (4-methoxyphenyl)-1- methyl piperidin-4-one oxime esters: Synthesis and a new insight into their antioxidant and antimicrobial potential. Med Chem Res 2014;23:1887-98.

Harini ST, Kumar HV, Rangaswamy J, Naik N. Synthesis, antioxidant and antimicrobial activity of novel vanillin derived piperidin-4-one oxime esters: Preponderant role of the phenyl ester substituents on the piperidin-4-one oxime core. Bioorg Med Chem Lett 2012;22:7588-92.

Harini ST, Kumar HV, Rangaswamy J, Naik N. Synthesis of thiazole-based substituted piperidinone oximes: Profiling of antioxidant and antimicrobial activity. Russ J Bioorg Chem 2017;43:186-96.

Karaman N, Oruc-Encir EE, Sicak Y, Catikkas H, Karakucuk A, Ozturk M, et al. Microwave-assisted synthesis of new sulfonylethidoxazines, screening of biological activities and investigation of structure-activity relationship. Med Chem Res 2016;25:1590-607.

Allen NS, Ortiz RA, Anderson GJ. Comparison of the thermal and light stabilising action of novel imine and piperazin binned hindered piperidine stabilisers in polyolefins. Polym Degrad Stab 1994;46:85-91.

Vasavirama K, Upender M. Piperine: A valuable alkaloid from Piper nigrum: A review. Int J Pharm Pharm Sci 2013;5:317-21.