Piperidine nucleus in the field of drug discovery

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Abstract
Background: Piperidine is an essential heterocyclic system and a pivotal cornerstone in the production of drugs. Piperidine byproducts showed several important pharmacophoric features and are being utilized in different therapeutic applications.
Main text: Piperidine derivatives are being utilized in different ways as anticancer, antiviral, antimalarial, antimicrobial, antifungal, antihypertension, analgesic, anti-inflammatory, anti-Alzheimer, antipsychotic and/or anticoagulant agents.
Conclusions: This review article sheds a light on the most recent studies proving the importance of piperidine nucleus in the field of drug discovery.
Keywords: Piperidine, Naturally occurring piperidines, Piperidine derivatives as anticancer agents, Piperidine derivatives as antivirals

Background
Heterocyclic compounds, mainly those bearing nitrogen are ubiquitous in nature and in medicaments as well. Most of them play important roles in the human body and have great biologic qualities.

Piperidine (Hexahydropyridine) (Fig. 1) is an organic heterocyclic amine widely used as a building block and reagent in synthesizing organic compounds, including medicinal products [1].

Piperidine derivatives represent a key and extensive category of nitrogen bearing heterocyclic compounds. Compounds with piperidine moiety show a wide variety of biologic activities. Piperidine is a vital fundament in the production of drugs. This nitrogen bearing heterocyclic ring system and its byproducts show several essential features and are being utilized in different ways as anticancer, antimicrobial, analgesic, anti-inflammatory, and antipsychotic agents. Piperidine and pyridine complexes comprehend two of the most common heterocyclic fragments present in FDA approved drugs [2].

Main text
Naturally occurring piperidine-based compounds
Piperine (N-acylpiperidine) (Fig. 2) is a true alkaloid having piperidine moiety, found in plants of Piperaceae family; it shows powerful antioxidant action because of its capability of hindering or suppressing free radicals. The pharmaceutical worth of Piperine is extensive because of its activity against cancer, inflammation, hypertension, and asthma [3]. Piperine was also found to have antidepressant like effects when given to mice with chronic mild stress [4]. On the other hand, the mechanism of action of Piperine is still not totally clear [5].

Nobuji et al. obtained diverse phenolic amides from pepper; those compounds showed reassuring anti-oxidation qualities in different assays. All of the amides displayed a positive antioxidation effect [6].

Several piperidine alkaloids isolated from natural herbs, were found to exhibit antiproliferation and antimetastatic effects on various types of cancers both
in vitro and in vivo for example Piperine (Fig. 2), Evolutionamine (Fig. 8), Matrine (Fig. 3), Berberine (Fig. 4) and Tetrandine (Fig. 5) [7].

Piperidine derivatives as anticancer agents
Cancer, uncontrolled cell growth, is a worldwide health matter that impacts a major proportion of the human population. These three malignant properties of cancer differentiate them from benign tumors, which are self-limited, do not invade or metastasize [8]. Cancer treatments have developed through recent years. Cancer treatments now include surgery, chemotherapy, radiotherapy, and modern approaches, namely interventional radiology, hormone therapy, and immunotherapy [9]. Anticancer medicines are categorized into groups according to their mechanism of action into alkylating agents, antimetabolites, anti-tumor antibiotics, topoisomerase inhibitors, and microtubule binding agents [10]. There are more than one hundred medically approved chemotherapeutic medications [11]. However, the toxicological data of most anticancer drugs have restrained their medicinal application as antiproliferative agents [10, 12]. In spite of the great achievements made in chemotherapy in recent years, resistance to conventional chemotherapeutic drugs and new targeted therapeutic agents is still a significant issue in cancer treatments and the cause of most recurrences [12–16]. Therefore, research of new anticancer agents with new mechanisms of action, high potency and low side effects is essential for chemists [8]. To diminish anticancer drugs' adverse effects upon normal cells, targeted cancer therapies are favored nowadays [17]. Targeted drugs block the growth and proliferation of cancer by interfering with specific molecules that are involved in the rise, advancement, and expansion of cancer without affecting normal cells [17]. Some chemotherapeutic agents have piperidine moiety within their structure, foremost among them, vinblastine and raloxifene.

Vinblastine (Fig. 6) is a plant alkaloid which is extracted from Vinca Rosea. This drug is an antineoplastic agent.
It is thought that the mechanism of action of Vinblastine is inhibition of mitosis at metaphase leading to mitotic arrest or cell death [18].

Raloxifene (Fig. 7) is second-generation selective estrogen receptor modulator (SERM). It is used for reducing the risk of invasive breast carcinoma in postmenopausal women by acting as estrogen blocker [19].

Evodiamine (Fig. 8) which is a quinolone alkaloid isolated from Evodia rutaecarpa was found to show anticancer effects in vivo and in vitro by induction of apoptosis or cell cycle arrest therefore preventing metastasis and angiogenesis [20–22].

Khairia et al. synthesized two piperidine analogues. These analogues were evaluated for their chemo preventive effect. Compound 1 (Fig. 9) was found to be the most potent chemo-preventive agent and could successfully decrease the number of cancer cells [23].

Suvankar et al. studied a series of twenty-five piperidine derivatives as free radical scavengers. These compounds exhibited a potent anticancer effect. Compound 2 (Fig. 10) was found to be the most potent antitumor agent. The mechanism of action was found to be binding to ctDNA via intercalation [24].

Amitabh et al. synthesized a novel series of piperidine derivatives and related aryl methyl ethers that were evaluated against MCF-7 breast cancer cell line and were found to have potent cytotoxic activity. Compounds 3a and 3b (Fig. 11) showed the highest efficiency. These compounds were tested against murine L1210, human HeLa, and CEM cell lines and demonstrated greater activity than both tamoxifen and raloxifene [25].

Yanqun et al. designed and synthesized a string of piperidine derivatives as new HSP70 inhibitors based on virtual library screening. Among these, compounds 4a–4e (Fig. 12) showed remarkable inhibitory effect on human breast cancer cells [26].
Jin et al. synthesized a series of \(N\)-(piperidine-4-yl) benzamide compounds and investigated their effect against cancer cells. Structure activity relationship showed that the presence of halogen, carboxyl, nitro, or methyl groups on ring B increased the cytotoxicity of the Piperidine derivatives. Compound 5 (Fig. 13) was found to have the maximum potency with an \(IC_{50}\) value 15-fold higher than Sorafenib [27].

Dong et al. prepared a series of new piperidine derivatives. These analogues were assessed for their anticancer activity. Compound 6 (Fig. 14) expressed strong antiproliferative activity by inhibiting the tubulin polymerization [28].

Xin et al. prepared a line of innovative 5-phenyl-N-piperidine ethanone-4,5-dihydropyrazole products. The novel compounds were evaluated for their anticancer activity. Among these, compound 7 (Fig. 15) exhibited maximum potency against SGC-7901 and MGC-803 cell lines. Structure activity relationship studies showed that Introduction of amide or nitro functional groups in place of trifluoromethyl group led to decreased anticancer activity [29].

Benaka et al. prepared a series of new diphenyl (piperidine-4-yl) methanol derivatives. These compounds were evaluated for their antiproliferative activity against HT-29, HeLa,16 MCF-7 and HepG2 cell lines via MTT assay. Compound 8 (Fig. 16) showed high cytotoxic activity against all cell lines. Structure activity relationship studies exhibited that increasing the carbon chain length reduced the antitumor activity, presence of hydrophobic groups (Cl, F) are essential for binding with the active site of the enzyme, and presence of electron donating groups (Cl, F) promotes the antitumor effect [30].

Debasish et al. synthesized a string of eight pyrenyl derivatives that were also screened for antiproliferative action. According to the \(IC_{50}\) data, compounds 9a and 9b (Fig. 17) were the most potent cytotoxic agents in the string. According to structure activity relationship analysis, using four carbon linker produced higher cytotoxic effect than five carbon linker[31].

Jin et al. developed a series of novel P2X7 receptor antagonists bearing piperidine moiety as possible antitumor agents. Among them, compounds 10, 11 and 12
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(Fig. 18) demonstrated highest cytotoxic effect against MDA-MB-231 breast cancer cell lines [32].

**Piperidine derivatives with antiviral activity**

Nikolai et al. synthesized a string of (R) and (S) isomers of novel adamantane-substituted piperidine analogs. Biologic tests of the produced compounds were carried out on the rimantadine-resistant S31N mutated strains of influenza A 2009(H1N1)pdm09 and modern pandemic strain 2016(H1N1)pdm09. The most powerful compounds were both enantiomers of the enol ester 13 (Fig. 19) exhibiting IC value equals to 7.7 µM with the 2016 Orenburg strain [33].

Guoxin et al. performed modifications on the structure of an original compound appointed from high throughput screening. A series of different analogues were prepared and were proved to have an inhibitory effect against influenza virus. Structure–activity relationship studies indicated that the ether linkage between quinoline and piperidine is crucial to the inhibitory effect. Compound 14 (Fig. 20) showed a superb inhibitory effect on a diversity of influenza virus strains and showed a good ability to interfere with the early to middle stages of influenza virus replication [34].
Piperidine derivatives with antimicrobial activity

AD et al. produced two piperidine derivatives. These derivatives were isolated from Streptomyces ficellus then evaluated for their antibacterial activity. Nojirimycin (Fig. 21) was found to be effective against S. lutea, S. aureus and E. coli. Nojirimycin is the prototype of a new class of antibiotics [35].

Chennan et al. prepared a string of piperidine-4-one oxime derivatives that was investigated for their in vitro antimicrobial activity. Compounds 15a and 15b (Fig. 22) exhibited strong antifungal activity against Aspergillus flavus and Candida-51, respectively. Compound 15b was found to be more effective than the reference drug; amphotericin B regarding MIC [36].

Jayaraman et al. synthesized a series of piperidone derivatives via Mannich reaction pathways. The compounds were evaluated for their antimicrobial effect against various types of bacteria and fungi. Compound 16a and 16b (Fig. 23) showed good antibacterial activity against B. subtilis, E. coli, K. pneumoniae and S. faecalis. Compound 17 and 16b (Fig. 23) showed good antifungal activity against A. niger, A flavus, C. neoformans, Candida 6 and Candida 51 [37].

Piperidine derivatives with antimalarial activity

Rokhyatou et al. designed and prepared novel 1,4 disubstituted piperidine derivatives that were tested for their activity against chloroquine sensitive and chloroquine resistant strains of P. falciparum. Compounds 18a–c (Fig. 24) were the most potent compounds among the prepared library [38].

Piperidine derivatives with antifungal activity

Zhigan et al. designed and synthesized a string of new antifungal piperidinyl triazole derivatives. Multiple compounds exhibited superb antifungal activity against a range of significant fungi. Among these compounds, compounds 19 and 20 (Fig. 25) were noticed to be highly active antifungal drugs [39].
Piperidine derivatives with antihypertension activity
Shamim et al. synthesized a string of novel N-substituted phenacyl piperidine derivatives that have been tested for their hypotensive activity. Compounds 21, 22a and 22b (Fig. 26) exhibited mild antihypertension activity. It was also discovered that the carboxamide group has no significant effects on arterial blood pressure and has no significant effect on blood pressure [40].

Yanjiang et al. tested compounds that were determined through screening of BMP2 up-regulators for their capacity to boost the expression of Inhibitor of DNA binding 1 (ID1) proteins. Depending on stem cell technology, they produced compound 23 (Fig. 27) as BMP upregulator that regulates BMP2 and PTGS2 levels, which may be worthwhile for treating pulmonary arterial hypertension [41].

SK et al. synthesized a novel piperidinyl urea derivatives that were tested for their activity as epoxide hydrolase inhibitors. Compound 24 (Fig. 28) was found to reduce the blood pressure effectively [42].

Piperidine derivatives with antiAlzheimer’s activity
Gunhild et al. studied the effect of Donepezil (Fig. 29) on the development of apathy and other neuropsychiatric disorders in patients with Alzheimer’s disease. It was proved that Donepezil could cause a great reduction of apathy that reached over 6 months and thus had a considerable favourable effect [43].
Khairia et al. designed and synthesized a string of novel piperidine derivatives that were evaluated for their inhibitory effect on acetylcholinesterase. These derivatives exhibited successful AchE inhibition, high selectivity and significant radical scavenging properties. Compound 25 (Fig. 30) exhibited high free radical scavenging effect [44].

Piperidine derivatives with analgesic and antiinflammatory activity
Adel prepared a series of piperidine derivatives that were tested for their antitumour activity against most of the human tumour cells. All the assessed compounds exposed significant antitumour properties against (HCT-116), (T-47D), (HL-60 (TB), MOLT-4, RPMI-8226) and (PC-3) cell lines. Of all the assessed compounds, compounds 26a–c (Fig. 31) showed substantial antiinflammatory properties [45].

Ahmed et al. synthesized a line of 2,4,6-trisubstituted-quinazoline derivatives bearing piperidine moiety. These compounds were tested for analgesic and antiinflammatory activity. Of all the compounds analyzed, compounds 27b, 27c and 27d (Fig. 32) were found to have higher analgesic effect than the standard drug indomethacin. Compounds 27a, 27b, 27c, 27e, 28 and 29 (Fig. 32) displayed both analgesic and antiinflammatory effects [46].

Piperidine derivatives with antipsychotic activity
Takeo et al. studied and investigated the antipsychotic effect of a novel piperidine derivative. Compound 30 (Fig. 33) was observed to have affinity to several dopamine receptors and exhibited atypical antipsychotic effect in animal models with limited prevalence of extrapyramidal adverse effects [47].

Ling et al. synthesized a series of new benzoxazole-piperidine derivatives with high affinity to dopamine D2, serotonin 5-HT1A and serotonin 5HT2A receptors. Among these derivatives, compound 31 (Fig. 34) was found to be a promising antipsychotic agent [48].

Xudong et al. designed and synthesised a line of piperidine derivatives. Among them, Compound 32 (Fig. 35) showed special pharmacological properties and a worthwhile pharmacokinetic profile and exhibited pro-cognitive properties. Compound 32 is thought to represent...
a new class of atypical antipsychotics for schizophrenia [49].

**Piperidine derivatives with anticoagulant activity**

Modesto et al. synthesized a line of 4-(piperidin-1-yl)pyridine derivatives. Structure activity relationship studies revealed that compound 33 (Fig. 36) exhibited strong factor IIa inhibition and showed good anticoagulant effect [50].

Akiyoshi et al. designed, prepared and investigated two racemic piperidine diamine derivatives. Compounds 34a–e (Fig. 37) expressed great inhibitory effect on factor Xa and displayed a great anticoagulant activity [51].

Khairia et al. designed and prepared a series of carbamoylpyridine and carbamoylpiperidine derivatives. These derivatives were investigated for their platelet aggregation inhibition effect. Among them, compounds 35 and 36 (Fig. 38) were identified to be the most potent antiplatelet aggregation agents [52].

**Conclusions**

This review mentions the potentiality of piperidine moiety accompanied with other molecular fragments in ameliorating various disease conditions. Naturally occurring piperidines were able to display extensive effects against cancer, inflammation, hypertension and sometimes behave as antioxidants. On the other hand, Synthetic piperidine derivatives that were presented in many research studies proved their potentiality as anticancer agents, antiviral, antimicrobial, antimalarial and antifungal agents. Also, piperidine derivatives can be designed and synthesized to exhibit additional biological effects as antihypertension, anti-Alzheimer’s, analgesic, anti-inflammatory, antipsychotic and anticoagulant activity.
Abbreviations

FDA: Food and Drug Administration; SERM: Second-generation selective estrogen receptor modulator; ctDNA: Cell-free circulating tumor DNA; MCF-7: Type of breast cancer cell line; murine L1210: Type of leukemia cell line; human HeLa: Type of cervical cancer cell lines; CEM: Type of leukemia cancer cell lines; HSP70: Heat Shock Protein Coding gene; SGC-7901: Type of human gastric cancer cell lines; MGC-803: Type of human gastric cancer cell lines; HT-29: Type of human colorectal adenocarcinoma cell lines; HepG2: Type of human liver cancer cell lines; MTT: 3-(4,5-Dimethylthiazol-2-yl)-2,5-diphenyl-2H-tetrazolium bromide assay; P2X7: P2X7 receptor; MDA-MB-231: Type of human breast adenocarcinoma cell lines; BMF: Basic Metabolic Panel; PTGS: Post-transcriptional gene silencing; AChE: Acetylcholine Esterase; MOLT-4: Type of leukemia cancer cell lines; RPMI-8226: Human myeloma cell line; PC-3: Human prostate cancer cell line.

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Authors’ contributions
MMA collected the data and wrote the draft manuscript. IMF collected the data and wrote the draft manuscript. HIES revised the manuscript and supervised the whole work. All authors read and approved the final manuscript.

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